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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RECENT PSYCHOPHARMACOLOGICAL RESEARCH

Well over 200 papers reporting psychopharmacological research have been presented at conferences and meetings of scientific and professional societies held during the past months. The following pages present brief accounts of some of the studies reported and of a few symposia.

With one exception—the Workshop on Drug Therapy for Children—these notes were prepared by members of the PSC staff and in most cases were based on the investigators' oral presentations. A few, however, were taken from the authors' printed abstracts. Since no one from PSC was able to attend the Workshop on Drug Therapy for Children, Dr. Lytton, who chaired the Workshop, was asked to prepare a summary for the PSC *Bulletin*.

These reports are intended as reportorial accounts of the studies presented, with no implication of evaluation or endorsement of the results or conclusions presented by the speakers, and without review by the investigators whose work is described. No attempt has been made to include all points mentioned by the speakers, or to present detailed coverage of each meeting. The primary objective is to give scientists a general overview of recently reported research in this field.

Many of the papers mentioned here will eventually be published in the scientific journals. In the meantime, inquiries about the work described should be directed to the investigators who carried out the research rather than to the PSC.

Federation of American Societies for Experimental Biology

The 44th annual meeting of the Federation of American Societies for Experimental Biology was held in Chicago April 11-15. It was a big enthusiastic meeting with over 10,000 registrants and a program of more than 2,600 individual papers. Of these, 126 were of direct psychopharmacological interest.

The New or Nearly New Drugs

A number of papers reported pharmacological studies of some of the newer drugs. Two series of compounds based on novel variations of the phenothiazine nucleus were of particular interest as possible forerunners of a new series of tranquilizers. Glassman et al. reported that the replacement of sulfur by selenium resulted in substances whose pharmacological properties generally paralleled those of their phenothiazine analogues. The phenoselenazines analogous to promazine and chlorpromazine showed the same type of cardiovascular, adrenolytic, and antihistaminic activity as the parent compounds. They were also similar in their potentiation of barbiturate sleeping time and in protection against epinephrine-induced pulmonary edema. Quantitatively, the presence of selenium enhanced antihistamine potency at the expense of ataractic activity.

Peck et al. presented data on the toxicity of three thiaxanthenes which in this case may be regarded as derived from the corresponding phenothiazines by the replacement of the ring nitrogen by carbon. The three compounds were administered orally to dogs in daily doses of 5, 10, or 20 mg./kg. After a few weeks, 2-chloro-10-(3-dimethylaminopropylidene)-thiaxanthene, a chlorpromazine analogue, produced reversible leukopenia and other hematological changes. In addition, the diethyl-aminopropylidene derivative was hepatotoxic, while the dimethylaminopropyl compound was cardiotoxic without causing blood dyscrasias. The author emphasized that comparatively small changes in molecular structure could result in marked alterations in toxicity.

In behavioral studies, Nash et al. found that 2-chloro-10-{3-[1-(3-hydroxpropyl)-4-piperazinyl] propyl}thiaxanthene (known as S. 9-888) and several related compounds inhibited the

conditioned avoidance response in the albino rat. The hydroxypropyl compound was shown to have antiemetic and minimal adrenergic blocking activities, and to inhibit motor function less than the other analogues tested (e.g., the hydroxyethyl compound). In clinical studies, also, the dyskinesias produced by the propyl derivative were minimal when compared with the ethyl derivative.

Bagdon described the results of toxicity studies of methaminodiazepoxide (Librium), and Keith et al. presented data on the anticonvulsant properties of the drug. Although it was slightly less active than phenobarbital sodium or diphenylhydantoin sodium against supramaximal electroshock seizures in mice, it was more effective than either against pentylenetetrazol-induced convulsions. In the minimal electroshock test, the activity of methaminodiazepoxide was intermediate between that of phenobarbital and diphenylhydantoin. The duration of action of a single dose in mice exceeded 5 hours.

The pharmacological properties of amphenidone, a "tranquilizer" just recently introduced on the market, were discussed in a paper by Reinhard et al. Amphenidone antagonized both electrically and chemically induced seizures in animals. Its anticonvulsant potency, particularly with respect to pentylenetetrazol, approached that of standard anticonvulsant drugs. Amphenidone also blocked the stimulant effects of intracerebrally injected LSD. Its analgesic potency was about one-third that of codeine. Sedative or hypnotic activity could be demonstrated only in rodents, and then only at lethal doses. Polysynaptic reflexes were depressed without significantly affecting monosynaptic reflexes. Spinal cord depressant activity was similar to, but longer acting than, that produced by mephenesin. The authors concluded that the drug had selective effects on the central nervous system. In a paper on the toxicology of amphenidone, Plekss and co-authors stated that the pattern of toxicity of the drug confirmed involvement of the central nervous system.

Based on their experience with 44 selected patients, Nodine and co-workers concluded that amphenidone is a mild to moderately potent ataractic agent, suitable for outpatient administration.

A new nonconvulsant stimulant, 5-phenyl-2-imino-4-oxo-oxazolidine, or FWH-352, has been shown to be intermediate between caffeine and amphetamine in its effect on spontaneous motor activity, and to have a mode of action on the central nervous system which resembles that of amphetamine. As described by McColl and Rice, it antagonizes reserpine-induced motor depression and alcohol-induced hypnosis. Compared to iproniazid, FWH-352 had less effect on hexobarbital sleep prolongation and on amine oxidase inhibition.

Both animal tests and preliminary studies in patients have shown that the deanol congener N-methyl, N-ethyl-2-aminoethanol (Riker 566) is a more potent stimulant than deanol itself. Compared to deanol, Riker 566 produced earlier spontaneous seizures in mice and rats following chronic oral administration; in mice, it lowered the pentylenetetrazol convulsive threshold to a greater extent; and it was 200 to 300 per cent more effective in increasing electrogenesis in trained, unanesthetized rabbits.

Two nonhydrazine inhibitors of monoamine oxidase (MAO) were also discussed. Spencer et al. reported on the cardiovascular effects of tranylcypromine (SKF 385). In the anesthetized animal, initial intravenous administration of the drug caused a rise in blood pressure, presumably by a peripheral mechanism since it could be blocked by dibenzyline. Subsequent doses, however, produced a sustained hypotension in the presence of unaltered responsiveness to sympathetic ganglionic stimulation or to epinephrine or norepinephrine injection. Investigation of mean arterial blood pressure in the unanesthetized dog showed a rise on intravenous administration of tranylcypromine, followed by a drop of pressure. After oral doses, only the depressor effects were seen, with onset at about 24 hours and a duration of approximately 72 hours. The effects of tranylcypromine and other MAO inhibitors and substrates on evoked potentials in the unanesthetized cat were presented in a paper by Revzin and Costa.

Taylor et al. described A-19120, or N-methyl-N-benzyl-2-propynylamine, as one of a series of potent nonhydrazine MAO inhibitors of the "nonreversible" type. In vitro studies

using rat liver mitochondria demonstrated its direct effect on the enzyme, and single doses in mice inhibited MAO activity for at least ten days. Rats receiving oral doses for several months showed 80 and 90 per cent inhibition, respectively, of liver and brain MAO activity.

Roszkowski and Govier reported investigations of α-methyl-β-ethylvaleramide (McN-X-181), a compound which has central-acting, muscle-relaxant properties and also affects behavioral responses. It preferentially inhibited polysynaptic, rather than monosynaptic, reflex pathways in the spinal cord. It had a taming effect on naturally belligerent cats and monkeys, and blocked fighting in paired preselected belligerent mice, all at doses well below the paralytic dose. This drug also blocked conditioned responses, secondary conditioned responses, and unconditioned responses. It has been tried clinically and may be useful in anxiety-tension states.

Carroll et al. reported on AHR-438–5-(3,5-dimethylphenoxymethyl)-2-oxazolidinone–a new oxazolidinone with muscle-relaxant, analgesic, and anticonvulsant properties. This compound has only minimal sedative, ataractic, or hypnotic activity.

A report on the hypnotic drug thalidomide–α-(N-phthalimido) glutarimide–which exerts a number of interesting synergistic effects with other central nervous system drugs, was presented by Kuhn and Van Maanen. Although oral doses of 100 mg. produce hypnosis in man, these investigators reported that in mice and dogs intraperitoneal doses of the drug produced only mild symptoms of CNS depression in mice and dogs, and caused no loss of righting reflex, even at doses (in mice) of 4000 mg./kg. As little as 30 mg./kg., however, significantly prolonged barbital and hexobarbital sleeping time. Although thalidomide had no anticonvulsant activity as measured by the maximal electroshock procedure, it potentiated both phenobarbital and diphenylhydantoin. It did not block conditioned avoidance responses in rats, but rather it enhanced this effect and the CNS depressant action of chlorpromazine.

Drug Metabolism

A number of papers described the metabolic fate of individual psychopharmacological agents. The one by Conney et al. contained data of considerable general theoretical interest. They found that pretreatment of rats for several days with a variety of drugs, e.g., phenobarbital, barbital, phenylbutazone, resulted in an increased rate of in vitro metabolism of these drugs by liver microsomal enzymes. This increase was paralleled by the appearance, in the intact animal, of a shortened duration of drug action. Furthermore, pretreatment with a given substance was shown to influence the metabolic rate of not only that compound, but also of selected other compounds. For example, pretreatment of rats with 3,4-benzpyrene stimulated the zoxazolamine-destroying enzyme of the liver and shortened the duration of paralysis in the intact animal, but it had no effect on hexobarbital hypnosis. Pretreatment with chlorcyclizine, on the other hand, affected the action of both zoxazolamine and hexobarbital. These findings may have a bearing on the pharmacological activity of drugs which are given over long periods of time, either alone or in combinations.

Also of general interest was the demonstration by Dixon and Fouts that starvation in mice produced a depression of enzyme activity in liver microsomes, and that this was general for oxidative enzyme pathways. Reductive enzyme systems were not affected. The suppression of oxidation could not be reversed by pretreatment with the test drug. For example, hexobarbital given 12 hours before sacrifice of the starved mice failed to raise the rate of hexobarbital metabolism above that of starved, non-pretreated animals. The effects of starvation were reversible, and enzyme activity returned to normal after 24 hours of feeding.

Gillette, in studies designed to elucidate the slow onset of action of imipramine, an antidepressive that is neither a direct stimulant nor an MAO inhibitor, stated that the drug readily enters rabbit brain and is localized selectively in certain areas. The drug disappears from the animal body in 6 or 8 hours, and little unchanged drug is excreted. The liver microsomal system metabolizing imipramine requires both TPNH and oxygen. Studies of imipramine metabolism in man are also under way.

Isotopically labeled deanol (2-dimethylaminoethanol-1,2-C^{14}) was shown by Small and Sakami to be converted by rat liver extracts to dimethylglycine-C^{14} in a reaction system stimulated by methylene blue and inhibited by phenazine methosulfate. No labeled sarcosine was formed, nor was there any evidence that preformed choline-C^{14} was converted to dimethylglycine-C^{14}.

Studies of isocarboxazid labeled with C^{14} in the benzyl group were conducted by Schwartz, who reported that the drug is metabolized by hydrolytic cleavage to form benzylhydrazine. This compound is then excreted in the urine largely in oxidized form as benzoic acid conjugated to form hippurate.

Meprobamate labeled with C^{14} in the carbonyl group was reported by Wiser and Seifter to be converted by rats, dogs, and man into at least four other substances: unchanged meprobamate, hydroxymeprobamate, the glucuronic acid conjugates of both meprobamate and hydroxymeprobamate, and an as yet incompletely identified hydroxylated compound.

Geller and Eiduson studied thioridazine excretion patterns in man after single and multiple administrations of both plain and delayed-action dosage forms of the drug. Peak excretion with single doses of these two forms occurred at 20 and 40 hours, respectively, after administration. After one week, drug excretion could no longer be detected. On continuous administration of thioridazine, peak excretion occurred after two to three weeks and then leveled off.

Behavioral Studies and Methodologies

Pauls et al. and Wilfon et al. presented papers on a new animal-behavior measure dubbed the "pernicious preening" test. The application of a pilo-cohesive such as "Magic Marker" to the fur leads to predictable persistent, intense, preening activity in mice and perhaps monkeys, but not in rats. The unremitting tearing of fur can be prevented by pretreatment of the mice with potent analgesics and with phenothiazines of established ataractic potency. The limits of the method were explored in tests using a variety of drugs of different pharmacological activities.

Using a modification of the Yen method for developing attack behavior in mice, the ED_{50} for antagonizing this response was determined for chlorpromazine, imipramine, meprobamate, and other psychopharmacological agents. In reporting this work, Cook and Weidley emphasized their interesting observation that attack behavior developed in animals regardless of whether their isolation cages were of solid metal, or clear plastic which permitted a view of neighboring mice, or of wire mesh which allowed both sight and touch.

Swinyard et al., exploring factors influencing amphetamine toxicity in aggregated mice, used pentylenetetrazol convulsive threshold to measure the relative CNS excitability of aggregated and isolated mice. Isolation had no effect on the threshold, while aggregation lowered it. It was also observed, however, that animals easily adapted to aggregation, at which point the effect disappeared. In all mice, amphetamine lowered the pentylenetetrazol threshold about 45 per cent. It was more lethal only in those aggregated mice which had not adapted.

In a paper concerned with screening drugs for suitability as daytime sedatives, Weaver and Miya presented data to demonstrate the utility of simultaneously measuring the changes produced in spontaneous motor activity (photocell activity cage) and in neurological proficiency (rolling roller performance).

Several papers dealt with drug effects on various kinds of conditioned behavior. Barry et al. reported on the effects of drugs on operant behavior during gradations in fear. Food-deprived rats were trained on a variable interval schedule to press a bar for food. The test situation was then modified to include electric shocks of various types, correlated in intensity to the loudness of a tone signal. The rate of bar pressing for food was increased by pretreatment with sodium amobarbital, chlorpromazine, and methamphetamine, unchanged by LSD, and variably affected by alcohol.

Ray and Marrazzi demonstrated that in rats chlorpromazine pretreatment, in doses too small to have an effect on performance, antagonized the LSD-induced depression of lever pressing for a water reward. It was of interest to note that high doses of chlorpromazine (30 to 40 times as much as the pretreatment dose) in themselves produced an LSD-like behavioral effect as well as a synaptic effect.

Neurological and Neurophysiological Studies

From a study of the effects of histamine on transcallosally evoked potentials in the cat, Gilfoil et al. reported that histamine injected intracarotidly appeared to be a potential cerebral synaptic inhibitor of the order of potency of serotonin or better. The specificity of the inhibition was demonstrated by its complete abolition by the antihistaminic drug tripelennamine.

It is known that prototype depressant substances such as mephenesin, carbon dioxide, and pentobarbital show marked differences in their selectivity for spinal monosynaptic and polysynaptic responses. According to Esplin, it appears from a variety of spinal cord experiments that drug-induced depression may involve either or both of two different mechanisms: depression of excitation as such, and depression of synaptic recovery. The selective depression of polysynaptic responses may therefore follow from depression of synaptic recovery and the attendant reduction of repetitive interneuron discharges.

Fox's paper reported that low doses of intravenously administered LSD produced significant changes in the evoked potentials from light flashes, in cats with electrodes either chronically or acutely implanted in the lateral geniculate body. The injection of schizoprenic serum blocked the changes, according to Fox, in 13 of 15 acute and 7 of 8 chronic preparations. The nonschizophrenic serum showed this blocking property in only 1 of 15 cases.

Biochemical Investigations

Measurement of norepinephrine and serotonin brain levels in newborn and young adult animals have led to interesting observations on the relationship of these substances to ontogenetic development. As described by Karki et al., newborn rats which show poorly developed behavior patterns have relatively low brain concentrations of these substances when compared to 10-week-old rats. Brain concentrations of newborn guinea pigs, on the other hand, are almost at an adult level and are paralleled by well-developed behavior patterns.

Frohman et al. described continuing experiments aimed at the isolation and characterization of a schizophrenic serum factor, using as an assay technique the effect of the factor on the carbohydrate metabolism of chicken erythrocytes.

Smith and Wortis, using pretreatment with iproniazid to inhibit MAO, studied alternate pathways of amine oxidation in the rat. Normetanephrine-1-C^{14} was shown to be metabolized under these conditions by irreversible acetylation to N-acetylnormetanephrine and excreted in the urine largely as the glucuronide of this compound.

Kakimoto and Armstrong showed that pretreatment of rabbits with MAO inhibitors increased in tissues and urine the concentration of octopamine, a precursor of parahydroxymandelic acid.

Titus et al. measured the uptake of catecholamines by brain slices from normal and reserpinized cats in experiments to elucidate the nature of the binding sites. The uptake of tritium-labeled D,L-epinephrine was measurably inhibited in the reserpine pretreated brains.

Cohn and Shore compared the effects of various MAO inhibitors on MAO as well as on diamine oxidase in the light of variations in the chemical structure of these drugs. Such compounds as iproniazid, containing a hydrazine moiety, inhibited both enzymes in vivo and in vitro. Those which were not hydrazine derivatives, e.g., tranylcypromine, affected only MAO. It was interesting to note, furthermore, that certain hydrazines such as isoniazid and hydralazine, inhibited only diamine oxidase.

In light of the importance attached to the relative extent of MAO inhibition in brain and in liver by various MAO inhibiting drugs, it was interesting to note the results of Horita's experiments. When rats were given either subcutaneous, oral, or intravenous doses, it was found that regardless of the route of administration iproniazid and nialamide consistently produced greater inhibition of the liver enzyme. On the other hand, pheniprazine and phenelzine, for example, showed preferential inhibition of brain MAO when given subcutaneously and liver MAO when given by mouth.

In experiments on the mechanism of action of reserpine, Orlans et al. found a close relationship between the appearance of sedation in rats and the loss of brain serotonin. Cold-stressed, reserpinized rats remained unsedated in spite of brain norepinephrine depletion as long as brain serotonin levels remained at normal levels. As the animals were brought to room temperature, there was a slow decrease in brain serotonin, with sedation occurring when serotonin levels reached about 50 per cent of normal. Along similar lines, Costa and Pscheidt found that in rats the degree of reserpine-induced ptosis observed was correlated to the serotonin but not to the catecholamine contents of the brain.

Authors and Titles of Papers

Listed below are the authors and titles of the 126 papers on psychopharmacological topics. Authors' addresses and abstracts of the papers may be found in *Federation Proceedings,* 1960, Volume 19, Number 1, Part I.

Adler, Martin W. Influence of brain lesions on sensitivity of amphetamine as measured by spontaneous locomotor activity.

Aprison, M.H. Effect of 5-hydroxytryptamine on cholinesterase activity.

Ausman, R.K., Davis, R.B., Meeker, W.R., and McQuarrie, D.G. Effect of amine oxidase inhibitors on *E. coli endoxtoxin* mortality in mice.

Bagdon, R.E. Toxicity studies of methaminodiazepoxide hydrochloride.

Barry, Herbert III, Wagner, Sylvia, and Miller, Neal E. Effects of drugs on rate of operant behavior during gradations in fear.

Baxter, Claude F., and Roberts, Eugene. Elevation of γ-aminobutyric acid (GABA) in brain with hydroxylamine (NH_2OH).

Beecher, Henry K. Further evidence for the increased effectiveness of placebos and "active" drugs with increased stress.

Bergen, J.R., and Pincus, G.G. Steroid suppression of LSD induced behavior changes in rats.

Bilstad, James M., and Benson, Wilbur M. Assessment of effects of dopa and dopamine on the conditioned emotional response in rats

Brune, G. W. G., and Himwich, H. E. Effect of reserpine on urinary tryptamine and indole-3 acetic acid excretion in mental deficiency, schizophrenia and phenylpyruvic oligophrenia.

Buckley, Joseph P., Furgiuele, Angelo R., and Kinnard, William J. Pharmacology of beta-phenylisopropylhydrazine.

Burack, W. R., Weiner, N., and Hagen, P. Effect of reserpine on adrenal catecholamine and adenine nucleotides.

Campos, H. A. Role of central nervous system catecholamines in morphine hyperglycemia.

Carroll, M. N. Jr., Luten, W. R., and Southward, R. W. Pharmacology of a new oxazolidinone with anticonvulsant, analgetic and muscle relaxant properties.

Chen, Graham, and Bohner, Barbara. Influence of reserpine and bulbocapnine on tonic extensor seizures in mice.

Chorover, Stephan L. Effects of mescaline and chlorpromazine on two aspects of locomotor activity in rat.

Christensen, J. A., and Wase, A. W. Chlorpromazine and C^{14} acetate incorporation into fatty acids and cholesterol.

Cohn, V. H., Jr. and Shore, P. A. Effect of monoamine oxidase inhibitors on diamine oxidase (histaminase).

Conney, A. H., Michaelson, I. A., and Burns, J. J. Accelerated drug metabolism in rats pretreated with drugs.

Conrad, E. A. Inhibition of sound-induced running, clonus and tonus by various central nervous system depressants.

Cook, Leonard, and Weidley, Edwin. Effects of a series of psychopharmacological agents on isolation induced attack behavior in mice.

Corson, S. A., Corson, E. O'Leary, Dykman, R. A., Peters, J. E., Reese, W. G., and Seager, L. D. Effect of meprobamate on conditioned antidiuretic and electrolyte retention responses.

Costa, Erminio, and Pscheidt, Gordon R. Reserpine ptosis is unrelated to brain catecholamine levels.

Delgado, Jose M. R. Brain and social behavior in the monkey.

Deneau, G. A., and Seevers, M. H. Method for screening centrally-acting drugs in the intact rhesus monkey.

Dixon, Robert L., and Fouts, James R. Liver microsomal drug-enzyme activity after starvation.

Eckel, R. E. Effects of chlorpromazine on the red cell.

Emele, Jane Frances, Shanaman, John E., and Warren, Marshall R. Phenelzine--a neuropharmacological study.

Esplin, Don W. Aspects of depressant drug selectivity for spinal monosynaptic and polysynaptic responses.

Finger, K. F. Biochemical aspects of the action of nialamide.

Fleming, W. W., and Trendelenburg, U. Supersensitivity to norepinephrine after pretreatment with reserpine.

Fox, Stephen S. LSD alteration of optic potentials (cat lateral geniculate); block by schizophrenic serum.

Freedman, D. X. LSD-25 and brain serotonin in reserpinized rat.

Frohman, Charles, Latham, Kenneth, Czajkowski, Norbert, Beckett, Peter, and Gottlieb, Jacques. Serum factor in schizophrenia.

Funderburk, William H., and Drakontides, Anna B. Effects of nialamide on the electroencephalogram.

Geiger, A., Aguilar, V., Gombos, G., Scruggs, W., and Whitney, G. Effect of isoniazid and iproniazid on pathways of glucose utilization in the perfused brain.

Geller, Edward, and Eiduson, Samuel. Thioridazine excretion patterns after single and multiple doses.

Geller, Irving, and Seifter, Joseph. A conflict procedure for evaluation of drugs.

Gilfoil, Thomas M., Hart, E. Ross, and Marrazzi, Amedeo S. Cerebral synaptic inhibition by histamine.

Gillette, J. R., Dingell, J. V., and Quinn, G. P. Physiological distribution and metabolism of imipramine (Tofranil).

Glassman, Jerome M., Begany, Albert J., Pless, Harvey H., Hudyma, George M., and Seifter, Joseph. Pharmacology of some phenoselenazines.

Gluckman, Melvyn I. Cerebral free and bound serotonin (5HT) after iproniazid (IIH) and reserpine (R).

Gottlieb, L. S., Hazel, M., Broitman, S., and Zamcheck, N. Effects of chlorpromazine on a transplantable mouse mastocytoma.

Hagen, Paul, and Wallace, A. C. An effect of reserpine on growth and sexual maturation.

Healy, S. T., Jenney, E. H., Goldstein, L., and Pfeiffer, C. C. Stimulant effect of a deanol congener--Riker No. 566.

Hochstein, Paul, and Cohen, Gerald. Mechanism of the special sensitivity of brain to glycolytic inhibition by quinones and dihydric phenols.

Horita, A. Route of administration of hydrazines as a determinant in the selective inhibition of brain and liver monoamine oxidase.

Innes, Ian R. Sensitization of the nictitating membrane to sympathomimetic amines by reserpine.

Jenney, Elizabeth H. Drug effects on electroconvulsive inhibition of conditioned avoidance response in rats.

Johnson, G. E., and Sellers, E. A. Effects of reserpine, noradrenaline and inhibitors on the metabolic rate of rats.

Kabara, Jon J., McLaughlin, James T., and Riegel, Carol A. Effect of methylphenidate on mouse brain free cholesterol.

Kakimoto, Y., and Armstrong, M. D. Identification of octopamine in animals treated with monoamine oxidase inhibitors.

Karki, N. T., Kuntsman, R., and Brodie, B. B. Norepinephrine and serotonin brain levels at various stages of ontogenetic development.

Keith, E. F., and Ardoline, G. A. Anticonvulsant action of methaminodiazepoxide HCl.

Kelleher, Roger, T., Riddle, William C., and Cook, Leonard. A behavioral analysis of qualitative differences among phenothiazines.

Kiplinger, G. F., Spencer, Alice, and Kensler, C. J. Dose-effect relationship between drugs affecting the sympathetic nervous system and the degree of hepatic lipid infiltration produced by carbon tetrachloride in mice.

Kletzkin, Milton. Effects of carisoprodol on CNS activity.

Krueger, R. F., Lauck, D. E., Moffat, E., and Green, D. M. Effects of analgesics on the mescaline scratch response in mice.

Kuhn, W. L., and Van Maanen, E. F. Effects of thalidomide on central nervous system drugs.

Kuntzman, R., and Spector, S. Impairment of catecholamine binding sites in brain by reserpine.

Lewin, Jorge, and Esplin, Don W. Analysis of spinal excitatory action of pentylenetetrazol.

Ling, Alfred S. C., Krantz, John C., Jr., and Kurland, Albert A. Indoklon as an intravenous convulsant agent.

McColl, J. D., and Rice, W. B. A new stimulant, 5-phenyl-2-imino-4-oxo oxazolidine (FWH-352).

McIntyre, A. R., Williams, David E., and Humoller, F. L. Bioassay of 5-hydroxytryptamine on heart of Venus mercenaria.

Maiti, Ajit, and Domino, Edward F. Action of methylated xanthines on electrically evoked afterdischarge in the neuronally isolated dog cerebral cortex.

Malis, J. L., Brodie, D. A., and Moreno, O. M. Drug effects on behavior of self-stimulation monkeys.

Martin, George M., Manring, Daniel, and Benditt, Earl P. Experimental turpentine abscesses in aggressive and non-aggressive inbred strains of mice.

Masurat, Thomas, Rice, Edward G., Herndon, John F., and Greenberg, Samuel M. Action of chlorpromazine hydrochloride (SKF No. 2601-A) on yeast hexokinase.

Meites, Joseph, and Hopkins, T. F. Release of prolactin from the anterior pituitary by neurohormones, drugs, hypothalamic tissue and other agents.

Minz, Bruno. Effects of reserpine and iproniazid on hypothalamic neurosecretion.

Mirkin, B. L., and Cervoni, P. Reserpine induced alterations in the reactivity of an adrenergic effector system.

Moffat, E., Krueger, R. F., Pfeiffer, R. O., and Green, D. M. Effects of analgesics on audiogenic seizures in mice.

Moore, Joanne I., and Moran, Neil C. Effect of ephedrine on myocardial contractility in dogs pretreated with reserpine.

Nash, Joe B., Emerson, George A., Faust, John A., and Sahyun, Melville. Comparative effects of thiaxanthene analogues on the conditioned response in the rat.

Nodine, John H., Bodi, Tibor, Levy, Howard A., Siegler, Peter E., and Moyer, John H. Use of aminophenylpyridone as an ataractic agent in outpatients.

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Ochs, S., and Hunt, K. Nicotine and GABA on cortical transmission.

Olds, James, and Travis, Robert P. Spreading depression and self-stimulation.

Orlans, F. Barbara, Sulser, Fridolin, and Brodie, B. B. Depletion of brain norepinephrine by reserpine without producing sedation.

Osborne, Melville W., Woessner, Irene L., and Naeff, Katherine. Explanation of adrenergic potentiation and blockade by cholinergic mechanisms.

Ostfeld, A. M., and Coombs, A. Y. Antagonistic effects of methacholine on central and peripheral actions of hyoscine in man.

Pauls, John F., Wilfon, J. Gordon, and Kandel, Alexander. Controlled studies on pernicious preening test in mice.

Peck, Harold M., and McKinney, Samuel E. Hematologic alterations produced in the dog by administration of 2-chloro-10-(3-dimethylaminopropylidene)-thiaxanthine.

Pepeu, Giancarlo, and Giarman, Nicholas J. Effect of certain neuropharmacologic agents on brain acetylcholine.

Pfeiffer, C. C., Goldstein, L., and Jenney, E. H. Comparative electroencephalographic stimulant effect in man of deanol (Deaner), choline and amphetamine.

Plekss, O. J., Reinhard, J. F., and Scudi, J. V. Toxicology of amphenidone (Dornwal): a new psychopharmacological agent.

Premachandra, B. N., and Turner, C. W. Reserpine and thyroid activity in the pigeon.

Proler, Meyer, and Kellaway, Peter. Anatomical substratum of behavioral and convulsive phenomena produced by methionine sulfoximine in the cat.

Pscheidt, G. R., and Morpurgo, Clara. Comparison of chemical and biological determination of brain catecholamines.

Ray, Oakley S., and Marrazzi, Amedeo S. Antagonism of behavioral effects of lysergic acid diethylamide by pretreatment with chlorpromazine.

Reinhard, J. F., Plekss, O. J., and Scudi, J. V. Pharmacology of amphenidone (Dornwal): a new psychopharmacological agent.

Resnick, O., Hagopian, M., and Freeman, H. Alteration of epinephrine metabolism in man.

Revzin, Alvin M., and Costa, Erminio. Effects of monoamine oxidase substrates and inhibitors on evoked potentials.

Rickels, K., Ewing, J. H., and Fochler, F. Effects of amobarbital sodium and meprobamate on autonomic reactivity as measured by cardiovascular responses to the cold pressor stress.

Rogers, L. L., and Newton, Wm. A. Serum electrolytes in mentally retarded children fed l-glutamine.

Roizin, Leon, Kaufman, M. A., and Miles, Bruno. Short-term experiments with chlorpromazine in rats: I. Histologic studies.

Roszkowski, Adolph P., and Govier, William H. Behavioral and central muscle relaxant properties of α-methyl-β-ethylvaleramide.

Sankar, D. V. Siva. Biochemical aspects of "LSD-psychosis."

Schallek, William, and Jew, Naitan. Effects of methaminodiazepoxide HCl on "septal rats."

Schwartz, Morton A. Metabolism of isocarboxazid (Marplan) in the rat.

Sigg, E. B., Osborne, Melville, and Bindler, Elliot. Potentiation of adrenergic and cholinergic mechanisms with small doses of imipramine.

Small, G., and Sakami, W. Conversion of 2-dimethylaminoethanol to dimethylglycine in liver.

Smith, A., and Wortis, S. Formation and metabolism of N-acetylnormetanephrine in rats treated with iproniazid.

Smith, Carroll M., and Walaszek, Edward J. Interaction of lysergic acid diethylamide (LSD) with polypeptides which stimulate smooth muscle.

Spector, S., Kuntzman, R., Hirsch, C., and Brodie, B. B. Delayed arousal of reserpine-treated rabbits by monoamine oxidase inhibitors.

Spencer, J. N., Porter, M., Froehlich, H. L., and Wendel, H. Cardiovascular effects of tranylcypromine.

Stein, Larry. Self-selected brain stimulation reward thresholds modified by drugs.

Sulser, F., Watts, J., and Brodie, B. B. Antagonistic actions of imipramine (Tofranil) and reserpine on central nervous system.

Swinyard, E. A., Miyahara, J. T., Wolf, H. H., and Clark, L. D. Factors influencing amphetamine toxicity in aggregated mice.

Szara, S., Hearst, E., and Putney, F. Metabolism of hallucinogenic tryptamine derivatives.

Talwalker, P. K. Initiation and maintenance of milk secretion in the rat following chlorpromazine administration.

Taylor, J. D., Wykes, A. A., Gladish, Y. C., Martin, W. B., and Everett, G. M. A new non-hydrazide monoamine oxidase inhibitor (A-19120) (N-methyl-N-benzyl-2-propynylamine hydrochloride).

Tedeschi, David H., Tedeschi, Ralph E., and Fellows, Edwin J. Activity of various pharmacological agents as in vivo inhibitors of monoamine oxidase.

Thier, David, and Gravenstein, J. S. Thyroxine and reserpine on rate of atrial contraction.

Titus, Elwood, Wilson, Cedric W. M., and Dengler, Hans J. Inhibition of uptake of epinephrine in brain slices by reserpine.

Trendelenburg, U., and Fleming, W. W. Subsensitivity to certain sympathomimetics after pretreatment with reserpine.

Walz, D. T., and Maengwyn-Davies, G. D. Effect of TM-10, cocaine and reserpine on isoproterenol vasomotor reversal.

Weaver, James E., and Miya, T. S. Effects of certain central depressants on mice.

Weiner, N. Effect of chlorpromazine (CPZ) on levels of adenine nucleotides and creatine phosphate (CP) of brain.

Westermann, E. O., Maickel, R. P., and Brodie, B. B. Some biochemical effects of reserpine mediated by the pituitary.

Wikler, Abraham, Green, Phillip C., Smith, Herbert D., and Pescor, Frank T. Use of a benzimidazole derivative with potent morphine-like properties orally as a presumptive reinforcer in conditioning of drug-seeking behavior in rats.

Wilfon, J. Gordon, Pauls, John F., and Kandel, Alexander. Pernicious preening test for evaluation of psychotropic drugs.

Wiser, Robert, and Seifter, Joseph. Meprobamate metabolism.

Witkin, L. B., Maggio, M., O'Keefe, E., and Galdi, F. Some central stimulants in mice.

Yen, Helen C. Y., Silverman, Arthur J., and Salvatore, Anita. Iproniazid reinforcement of anticonvulsants.

Young, R., Kaplan, H. M., and Kaplan, M. R. Chlorpromazine premedication with pentobarbital anesthesia in the turtle.

Zsigmond, Elmer K., Foldes, Francis F., and Foldes, Vera. Lack of correlation between the psychopharmacologic and anticholinesterase effect of LSD and its congeners.

Symposium on Some Aspects of Central Nervous System Stimulants

The Medicinal Chemistry Section of the American Chemical Society meeting included a symposium on "Some Aspects of Central Nervous System Stimulants." The participants were Keith F. Killam, Stanford University School of Medicine, Palo Alto, California; Lowell O. Randall, Hoffmann-La Roche, Inc., Nutley, New Jersey; Ralph E. Tedeschi, Smith Kline & French Laboratories, Philadelphia, Pennsylvania; and John V. Kinross-Wright, Baylor University College of Medicine, Houston, Texas. The meeting was held in Cleveland, Ohio, on April 11 and 12, 1960.

The Division of Medicinal Chemistry employs the technique of presenting general review papers in specific areas of research to keep its members informed about recent developments in the pharmacology and clinical uses of drugs. This year's symposium on CNS stimulants included reviews of pharmacological, biochemical, and clinical aspects of a number of antidepressive drugs.

Killam reviewed his work on the influence of gamma-aminobutyric acid (GABA) on electrical activity within different regions of the brain. GABA has been described by other workers as a neurohormone, but most prefer to consider it a "modulator" of neurohormonal and electrical activity within the brain. Thiosemicarbazide ($NH_2.CS.NH.NH_2$) produces a lower level of GABA in brain and causes concurrent spontaneous epileptiform seizures. It also alters patterns of electrical activity from certain cerebral and cerebellar cells.

In his paper Killam referred to the work of Eugene Roberts (City of Hope Medical Center, Duarte, California), who has studied the reactions involved in the conversion of glutamic acid to GABA. The enzyme system which converts glutamic acid to GABA is inhibited by thiosemicarbazide. Inhibition of this system—which is apparently a decarboxylase enzyme—leads to convulsive seizures. If animals are administered thiosemicarbazide and the central nervous system is not stimulated, convulsive seizures are not exhibited. Killam contends that neuronal activity is essential for the firing of a seizure pattern, and that convulsive effects are not produced solely by low brain levels of GABA. Deaminase inhibitors are known that can increase brain GABA levels from 200 to 500 per cent, and it has been proposed that this increase may be associated with a kind of "tranquilization." Hydroxylamine injections increase brain GABA levels and make animals nonsusceptible to threshold electroshock. The role of gamma-aminobutyric acid in central nervous system function remains to be established.

The pharmacology of amine oxidase inhibitors, from iproniazid through compounds currently in clinical use, was reviewed by Randall. In the Hoffmann-La Roche drug screening program, in vitro and in vivo techniques have been used for the assessment of monoamine oxidase (MAO) inhibitors. Much significance has been attached to the fact that the psychostimulant effects of these compounds appear to be related to the elevation of biological amines (serotonin and norepinephrine) in the brain. Certain of the MAO inhibitors appear to gain access to the central nervous system preferentially and inhibit MAO to a greater degree than do other potent MAO inhibitors which act only on the enzymes in the liver and other tissues. In this review, it was proposed that the anti-anginal action, antihypertensive effects, and side effects of these drugs may be related to the accumulation of pharmacologically significant amines in peripheral tissues. The role which MAO plays in the central nervous system has not been clearly established; neither has anyone demonstrated the relationship between MAO inhibition and antidepressive activity in this class of compounds.

Tedeschi, with co-authors David H. Tedeschi and Edwin J. Fellows, presented a paper on the pharmacology of a number of arylcycloalkylamines. He described the work which led to the discovery of SKF 385, which is tranylcypromine (trans-2-phenylcyclopropylamine), a substance found to be a potent nonhydrazine MAO inhibitor and to elicit an antidepressive effect in man. These workers have observed that SKF 385 not only inhibits MAO but also potentiates subconvulsant doses of tryptamine in rats. (In suitable intravenous doses, tryptamine produces in a high percentage of rats clonic convulsive seizures involving rapid beating with the forepaws.) The tryptamine-potentiation effect has been used as a screening technique to evaluate the MAO inhibitory activity of a number of compounds. For example, when administered orally prior to the intravenous dose of tryptamine, iproniazid has an ED_{50} of 10 mg./kg. whereas SKF 385 has an ED_{50} of 0.18 mg./kg. The concept of using tryptamine is based upon the apparent role of MAO in the central nervous system. In an untreated animal, tryptamine is inactivated by MAO; unless MAO is inhibited, no measurable pharmacological effects will be produced by the subconvulsant dose of tryptamine. The evidence suggests that SKF 385 is a potent in vivo inhibitor of MAO.

The characteristic response of rabbits treated with SKF 385 and later injected with reserpine is a marked rise in rectal temperature and signs of central nervous system stimulation. Rabbits deeply sedated with reserpine are aroused from their stupor by the injection of tranylcypromine. It appears that this compound may find a place in the treatment of psychiatric depressions.

The clinical aspects of central nervous system stimulation were discussed by Kinross-Wright, who particularly stressed the need for more accurate diagnosis of the various clinical categories of depression. The ultimate value of the various classes of drugs designated central nervous system stimulants will, he suggested, depend upon the clinical label attached to the patients being treated. He felt that more accurate diagnosis might lead to more successful drug use. He also proposed a classification of the many drugs now known to influence the central nervous system, observing that psychotomimetic agents might also be considered central nervous system stimulants.

Section on Pharmacology and New Drugs, Pan American Medical Association

The Section on Pharmacology and New Drugs of the Pan American Medical Association met in Mexico City on May 6, 7, and 9 during the 35th annual meeting of the Association. The Section was presided over by Rafael Mendez, Head of the Department of Pharmacology of the National Institute of Cardiology in Mexico City.

The first session of the meeting was devoted to a panel discussion of the ethics of experimentation with human subjects. Henry K. Beecher of Harvard University was chairman of the panel. Representatives of the Canadian Food and Drug Administration, of several medical schools and State health departments in the United States, and of the medical departments of a number of U.S. and Latin American pharmaceutical firms participated in the discussions. As a result of the deliberations, it was proposed that a legal precedent is needed. A court trial involving a new drug evaluation could firmly establish the legality of this aspect of medical practice, strengthen the physician's position in evaluating new therapeutic agents, and legalize the research concept of testing new and potentially better drugs. The group observed that the present situation is incongruous: in the U.S., for example, a new drug cannot be marketed until it has been tested in human subjects and its safety has been established; on the other hand, trying unknown drugs in this way may be malpractice.

The participants noted that it is perhaps unfortunate that the 10 points established at the Nuremberg trials regarding the ethical use of humans for experimental purposes are coming to be accepted as a Western credo. It was generally agreed that the Nuremberg principles may not necessarily be the best possible medical "bill of rights," and that they should be carefully scrutinized. Beecher pointed out that certain people in our social system—for example, mountain climbers, speedboat racers, or others usually categorized as daring—would probably be willing to participate in scientific investigations involving an element of risk. He also mentioned other groups, among them the Mennonites and conscientious objectors, who have rendered an extraordinarily valuable service to their fellow men by volunteering as experimental subjects for evaluations of new drugs. Some participants expressed great confidence in studies in which medical students serve as subjects. Such investigations are especially valuable because the subjects have been trained to recognize symptoms and report them accurately.

The final point brought out in this discussion was the need for a firm, clearly stated journal publication policy requiring that reports of a new drug investigation include all accumulated information about new agents, covering the undesirable as well as the desirable aspects of their therapeutic use.

Papers of direct psychopharmacological interest were concentrated in the session on "brain acting drugs." An excellent report was presented by Ramon Naranjo, Professor of Pharmacology at the Province Medical School in Guadalajara, Mexico, who described an in vitro investigation of the effect of nialamide on biochemical mechanisms within the central nervous system. Experiences with nialamide in the treatment of chronic alcoholism were reported by Wenceslao Orozco, also from the Province Medical School in Guadalajara. He

found that patients who had been alcoholic for 5 to 34 years could be satisfactorily maintained on nialamide. Although none of the patients have completely abandoned the use of alcohol, the drug has prevented an increase in the frequency of bouts of acute alcoholism.

Reports on the theoretical background of the MAO inhibitors, their pharmacology, and their clinical use were presented by John Spencer of Hoffmann-La Roche, Inc., Nutley, New Jersey. Among the MAO inhibitors discussed by Spencer was RO-4-1038/1, which is serine isopropyl hydrazine. This compound, one of many synthesized in the Hoffmann-La Roche laboratories, is considered to be as effective as isocarboxazid (Marplan) in the treatment of depression, but much less effective than isocarboxazid in angina pectoris. A number of clinical studies have established that MAO inhibitors relieve the pain of angina pectoris, but the mechanism of action remains obscure. Animal experiments indicate that the MAO inhibitors may increase the oxygen utilization of heart muscle. Some work has suggested that these agents give rise to an increase in the catechol amine content of cardiac muscle. They are also ganglionic blocking agents. Since these drugs produce an elevation in mood, it has been proposed that they would be useful in angina, largely by causing the angina patient to be less anxious about impending cardiac pain. Workers in various laboratories disagree, however, about the usefulness and the mechanism of action of these drugs.

Maurice Tainter of the Sterling-Winthrop Research Institute, Rensselaer, New York, described the general pharmacology and clinical use of chlormethazanone (Trancopal in the U. S., Fenarol in Latin America). This drug, which has tranquilizing and muscle-relaxant properties, is well known in the U. S. and apparently enjoys wide clinical acceptance in the Latin American countries.

A film prepared by the Hoffmann-La Roche laboratories showed the taming effect of methaminodiazepoxide (Librium) on wild animals--the panther, wild Australian dog (dingo), Bengal tiger, and several varieties of Old World monkeys. The film, which was made in the San Diego zoo, illustrated very vividly the drug's ability to modify vicious, aggressive, assaultive behavior in these animals without producing marked ataxia or sleep, though it was frankly admitted that this taming effect may have little relevance to the action of the drug in psychiatric patients. However, in view of the fact that reserpine's similarly taming effect in the rhesus monkey has been widely cited as an example of "tranquilization," further experimentation with this drug in other types of animals was considered worth while. It was noted that new chemical substances of this type may produce unique, quantifiable changes in the behavior of some animals and that such changes may be analogous to behavioral changes in humans. A number of animal screening techniques have been devised that capitalize upon the peculiar characteristics of certain species of animals.

Quantitative electroencephalographic studies of rabbits following administration of deanol, atropine, choline, and amphetamine were described by Carlos Munoz, Professor of Pharmacology at the University of Chile in Santiago. The work was conducted in the Department of Pharmacology at Emory University, Georgia, where he is visiting scientist. The unique character of his experiments revolved around the use of an electronic device that converts EEG frequency signals to a quantitative numerical pattern, thus making it possible to count from different brain regions the number of positive and negative discharges occurring normally and after drug administration. Intravenous injection of deanol increased the number of these electric signals and produced an EEG pattern characterized by the spindling seen in the sleep pattern. Choline exerted a similar, slight effect of short duration. Choline injections followed by deanol administration appeared to exert antagonistic effects. Atropine, as expected, abolished the effect of deanol. The comparative effects of intravenous injections of choline, deanol, amphetamine, and saline on EEG tracings in man were also studied. Choline had very little influence. Deanol and amphetamine induced similar decreases in the total number of signals, but their effects were characterized by an increase

in the number of low voltage, fast activity discharges. In man, there was a 30-minute latency period before the maximal action of deanol was experienced, but the effect of amphetamine occurred almost immediately. Munoz and his co-workers believe that deanol is a drug which is capable of penetrating the blood-brain barrier. The fact that this chemical may form acetylcholine within the central nervous system may account for its pharmacological effects.

The remaining sessions were devoted to papers and discussions on the cardiovascular and renal systems, corticoids, and general pharmacology. The papers presented throughout the meeting seemed to reflect less concern about the use of drugs in mental illness than in life-threatening acute illnesses. Mental disease was singled out, however, as a clinical area in which better techniques are needed for the measurement of subjective responses to drugs.

Symposium on Quantitative Methods in Pharmacology

A number of new or improved statistical approaches to some of the classical research problems of pharmacology were presented at the Symposium on Quantitative Methods in Pharmacology. The symposium was held in Leyden, The Netherlands, on May 10 to 13, under sponsorship of the Biometric Society, a section of the International Union of Biological Sciences.

Proposed solutions to some of the methodological problems encountered in psychopharmacological research, as well as in other pharmacological work, were described in several papers. Dunnett, for example, in a paper concerned with drug-screening problems, described a method for computing critical rejection levels not only when two levels of drug activity exist (active and inactive), but also in cases when some drugs are more likely to be active than others and when more than two levels of activity may be involved.

In the session of papers on sequential analysis, P. Armitage (London School of Hygiene and Tropical Medicine), who chaired the session, discussed a number of refinements which have increased the sensitivity and versatility of sequential analysis. Rumke presented a design for testing, in animals, the difference between two treatments at optimal dose levels.

A method of comparing inter- and intraspecies sensitivity to drugs was proposed by Pelikan. He described a method of expressing dose as a power function of body weight, suggesting that this method would increase the precision of estimating and predicting drug potency among species or individuals, minimize interspecies variance in drug potency, and facilitate detection of species differences in sensitivity to drugs.

Two criteria of the validity of cross-over assays were put forward by Rerup. His paper emphasized that such assays are valid only when (1) a set of observations has been obtained in a given order and simultaneously in the reverse of that order, and (2) no significantly different changes in reaction between groups of subjects occur between treatments.

In a session on mixtures of drugs, Ariëns explored some of the problems involved in comparing results obtained with various drugs or with one drug under different conditions (e.g., different doses). He gave some examples of designs and methods for determining whether, to what degree, and in what sense the effects or magnitude of effects which are compared are really comparable.

Listed below are the authors and titles of these and other papers presented at the symposium:

Ariëns, E. J. (University of Nijmegen, The Netherlands). Analysis of the action of drugs and drug combinations.

Billewicz, W. Z. (University of Aberdeen, Scotland). A statistical investigation of factors affecting the accuracy of D_2O determinations by the falling drop method.

Brock N., and Schneider, B. (Asta Werke A. G., Brackwede, Germany). Pharmacological characterization of drugs by means of the therapeutic index.

D'Arcy, P. F., and Grimshaw, J. J. (Allen and Hanburys Ltd., Ware, England). Some problems arising in drug standardization and the selective screening of compounds of potential pharmacological interest.

de Jonge, H. (Netherlands Institute of Preventive Medicine, Leyden, The Netherlands). The influence of non-normality on the significance levels of Student's two sample test.

de Jongh, S. E. (University of Leyden, The Netherlands). Isoboles.

Dikstein, S. (The Hebrew University, Jerusalem, Israel). Physical chemistry of drug-receptor interaction.

Dufrenoy, J. (Conservatoire National des Arts et Métiers, Paris, France). Using the arc tangent scale for quantitative methods.

Dunnett, C. W. (American Cyanamid Company, Pearl River, New York, and University of Aberdeen, Scotland). Statistical theory of drug-screening.

Emmens, C. W. (University of Sydney, Australia). Biological assays involving quantal and semi-quantal responses.

Goldberg, L. J. (University of California, Berkeley, U. S. A.) A visual statistical approach to bio-assay.

Gurland, J. (Iowa State University, Ames, Iowa). Determination of minute insecticidal residues through biological assay.

Hajnal, J. (London School of Economics, England). Sequential tests on analgesics in rheumatoid arthritis.

Hemelrijk, J. (Technological University of Delft, The Netherlands). Experimental comparison of Student's and Wilcoxon's two sample tests.

Hewlett, P. S. (Pest Infestation Laboratory, Slough, England). Models for quantal responses to mixtures of two drugs.

Johnson, N. L. (University College, London, England). On the choice of a sequential test procedure.

Juvancz, I. (Mathematical Institute of the Hungarian Academy of Sciences, Budapest, Hungary). Contra-indication of nonparametric tests in medical experimentation.

Mathews, A. G. (Commonwealth Serum Laboratories, Victoria, Australia). The interpretation of antibiotic blood level curves.

Méwissen, D. J. (University of Liege, Belgium). Sequential tests on protective effects of cystamine and chlorpromazine.

Pelikan, E. W. (Boston University School of Medicine, U.S.A.). Dose metameters in comparative pharmacology.

Rerup, C. (The Royal University, Lund, Sweden). On the validity of a cross-over assay.

Rümke, Chr. L. (Free University of Amsterdam, The Netherlands). An efficient design for comparing the effects of two treatments.

Schneiderman, M. A. (National Cancer Institute, Bethesda, U.S.A., and London School of Hygiene and Tropical Medicine, England). Statistical problems in the search for an anti-cancer agent by the Federal Cancer Institute of the U.S.A.

Smith, K. L. (Boots Pure Drug Company Ltd., Nottingham, England). Sequential analysis applied to biological control tests for pharmacopoeial substances.

van der Vaart, H. R. (University of Leyden, The Netherlands). On the robustness of Wilcoxon's two sample test.

van Eeden, Constance (Mathematical Centre, Amsterdam, The Netherlands). On distribution-free bio-assay.

van Strik, R. (Philips-Duphar N. V., Weesp, The Netherlands). A simple method of estimating relative potency and its precision from semi-quantitative responses.

Eastern Psychological Association

At the April meetings of the Eastern Psychological Association "psychopharmacology" was almost synonymous with effects of drugs on animal behavior. Reports were given on many different kinds of drugs, on various kinds of animals, as measured by a wide range of techniques. There were no reports of animal screening of new drugs. The meeting seemed to reflect the current interest in examining in detail the effects of older drugs on many dif-

ferent kinds of behavioral measures. Operant conditioning techniques remain the most often used investigational approach.

Zimmerman and Schuster were interested in the interaction among the components of a multiple schedule with differential reinforcement of low rates (DRL). When rats were trained on schedules involving two DRL components, they were able to discriminate between them, and some interactions were observed. Acute administration of dl-amphetamine disrupted timing behavior, but did not eliminate the discrimination between the two components. In another experiment they investigated the effects of chronic administration of dl-amphetamine. They found that in the initial drug sessions timing behavior as measured by interresponse time was disrupted, but that with continued drug administration there was progressive recovery of the predrug performance. Because general activity levels remained high, an explanation of these results in terms of physiological tolerance was rejected.

Pigeons responding to a complex reinforcement schedule with fixed-interval, fixed-ratio, and mixed schedules were studied by Kelleher, Fry, and Cook. Chlorpromazine (2.5 to 5 mg./kg.), meprobamate (75 to 150 mg./kg.), and phenobarbital (20 to 40 mg./kg.) administered orally each gave increased response rates. However, at higher doses chlorpromazine decreased the rates, and phenobarbital abolished stimulus control. Davidson, Cook, and Kelleher also trained dogs to respond on a multiple fixed-interval, fixed-ratio schedule. Subcutaneous doses of chlorpromazine (0.125 to .5 mg./kg.) increased the response rates, but higher doses decreased them. Fixed-ratio response rates were decreased with subcutaneous doses of 0.25 to 4 mg./kg.; at higher doses, stimulus control was weakened but was generally present.

A three-ply multiple schedule was used by Heise, Walker, and Scheckel to measure the anti-appetite properties of amphetamine and other drugs in relation to "side effects" such as stimulation or depression. They used fixed-ratio, avoidance, and extinction components. The relationship between the appetite-reducing properties and the "side effects" was expressed as a ratio between the dose that reduced performance on the fixed-ratio component and the dose that affected avoidance performance.

Retention of a visual discrimination habit after administration of secobarbital and caffeine was tested by Pare. The drugs were injected five seconds, two minutes, and one hour after learning to criterion. Injections of secobarbital after five seconds and after two minutes resulted in significantly more errors on retention trials than injections after one hour. Caffeine, however, injected after five seconds significantly facilitated retention, but had no effect when administered after two minutes or one hour.

Blough used pigeons to study the effects of pentobarbital on visual discrimination and generalization. One group learned a simple intensity discrimination. Another group learned a simple wave-length discrimination, and also were given pre- and postdiscrimination spectral generalization tests. Pentobarbital greatly increased response rates that had been depressed by discrimination training, and, to a lesser extent, increased the gradients of generalization.

Many studies, perhaps because of the possible analogies with human behavior, were concerned with fear, conflict, and avoidance behavior. Williams and Miller described how they have automated measurement of the potentiating effects of fear on the startle response, and how this potentiated startle technique can be applied to psychopharmacological work. They have found that alcohol depresses the potentiated startle response, and that methamphetamine increases it. They also presented dose-response and time-course data. Conditioned suppression (unavoidable shock on grid) and conflict (shock on bar) were compared by Barry and Wagner as measures of drug effects. With both techniques a sensitive measure was obtained by using as the conditioned stimulus a gradually increasing tone, the loudness of which was correlated with intensity of the shock.

In a study of the effects of chlorpromazine and perphenazine on bar-pressing in an approach-avoidance conflict situation, Grossman found an inverse relationship between bar-

pressing and fear intensity. Both chlorpromazine and perphenazine depressed nonfear performance, but increased performance above the control rate during all levels of fear.

Edwards, Harris, and Marlin's study was designed to compare drug-induced catalepsy with loss of avoidance behavior. They tested conditioned avoidance (a warning light and noise preceded grid shock), unconditioned avoidance, and cataleptic behavior in rats that had received phenobarbital, chlorpromazine, reserpine, morphine, bulbocapnine, scopolamine, or chlormezanone. All the drugs blocked conditioned avoidance in varying degrees. Neither scopolamine nor phenobarbital blocked unconditioned avoidance, but the other drugs did. And bulbocapnine, chlorpromazine, reserpine, and morphine produced catalepsy. The investigators concluded that strong tranquilizers and analgesics, which specifically block avoidance, are potent cataleptic agents.

The conditioned avoidance response was blocked to a greater extent by chlorpromazine than by mescaline, according to a study reported by Chorover. An analysis of intertrial activity also showed that locomotion was reduced by chlorpromazine but increased by mescaline, suggesting that the chlorpromazine and mescaline impairments differ in kind.

Geller and Seifter presented their new conflict procedure for the evaluation of drugs. They imposed a conflict situation on a variable-interval base line by simultaneously giving a food reward and a mild shock with every lever response to a discriminative stimulus. Pentobarbital, phenobarbital, and meprobamate each increased lever pressing in the presence of the stimulus, but promazine and amphetamine decreased responding.

In Carlton's study, atropine disrupted the characteristic behavior pattern of rats working under a Sidman avoidance schedule, but it did not consistently depress the rate of avoidance responding.

Feldman and Bremner gave phenelzine to rats inmediately after sessions on a Lashley jumping stand with a stressful, insoluble problem. When tested subsequently on a soluble problem, the rats showed less fixation formation than a group of no-drug controls and rats that had been tested, in earlier experiments, after receiving tranquilizing drugs, barbiturates, other energizers, or alcohol. These results are similar to those obtained with electroconvulsive shock.

Black and Adamson hypothesized that alcohol should improve performance in an avoidance-avoidance learning task in which rats were required to jump a barrier they had previously been taught to avoid. The hypothesis was confirmed, and was related to an interpretation that alcohol has a general tension-reducing effect. Testing the effect of a Sidman avoidance procedure on alcohol consumption in the rhesus monkey, Clark and Polish found that during avoidance training alcohol intake increased but water intake remained the same or decreased. Myers studied the effects of varying doses of alcohol on differential lever pressing in the rat by testing preference for food, water, or alcohol. Both learning and preferences were affected, but not retention of responses after prolonged drinking. Otis and Berkley reported on the effects of chlorpromazine, reserpine, and meprobamate on the water-ingestion response in the rat. Mean duration of individual tongue laps, mean duration of intervals between laps, rate of lapping, and amount of water ingested after a period of water deprivation were different under the three drugs.

By use of a modified self-stimulation technique in which animals could self-select their threshold for rewarding brain stimulation, Stein showed that reward thresholds for hypothalamic and tegmental stimulation were raised by chlorpromazine and reserpine and lowered by stimulants of the amphetamine class. As part of his study of sensory deprivation and response rates, Fox found that increasing light deprivation and injections of amphetamine both increased rate of response. Barnes studied mice under isolation and found that trifluoperazine was the most effective tranquilizer under the conditions used.

Schnitzer and Ross were interested in finding some of the important variables of loco-

motor activity. Using mice in a photocell apparatus, they found that a determination of the time-action course of drugs gave more complicated, but also more complete, information than the discovery of mere dose-response relationships. The drugs used were amphetamine and pentobarbital; a group given physiological saline and an untreated group served as controls. Interestingly, the saline solution, in the volumes used, depressed activity, thus suggesting that these animals should not be considered "normal" control animals.

Waller and Waller investigated the effects of chlorpromazine on escape learning. They used a subspecies of deermice which characteristically show maladaptive behavior when placed on an electrified grid; instead of running to a safe area, they leap wildly about the electrified floor and return to it after escaping to the safe part of the apparatus. Chlorpromazine had a pronounced effect on the learning curves, but not on performance after it was stabilized. The results also showed, however, that although the drug interferes with learning, the kind of practice the animal has while receiving the drug affects performance after the drug is withdrawn.

Ross and McGaugh reported a study of the retroactive effects of strychnine on maze learning of rats. Using rats of the S1 and S3 strains (one "maze-bright," the other "maze-dull"), they injected strychnine one minute or one hour after each daily trial. When injected one minute after the trial, strychnine facilitated learning in both groups of rats. However, when the drug was injected one hour after the trial it had no effect on learning in the "dull" rats but improved learning in the "bright" rats.

In the reports of studies with human beings, Snapper, Mechner, and Ray described their development of behavioral procedures that may lead to more meaningful comparisons of drug effects in animals and in man. Two subjects worked for monetary reinforcement on a seven-component multiple schedule. The components were (1) fixed minimal interval, (2) a modification of the fixed minimal interval, (3) Sidman avoidance schedule, (4) a three-member chain, each member a fixed minimal-interval cycle, (5) fixed consecutive number, (6) fixed interval, and (7) fixed number. Time courses of stimulant drugs as measured by these procedures were presented.

Mirsky and Cardon presented a comparison of EEG and finger pulse changes that accompanied impaired attention following prolonged sleep deprivation and chlorpromazine. Simultaneous study was made of changes in performance on a visual and auditory version of the continuous performance task, the EEG, and the finger plethysmogram, after 72 hours of sleep deprivation, and 3 hours after receiving 200 mg. of chlorpromazine. Both conditions produced performance degradation, but errors after sleep deprivation were accompanied by marked EEG and finger pulse changes, while errors following chlorpromazine were not.

The effects of meprobamate on several finger dexterity tasks of varying difficulty were tested by Chambers and Upton. They used such tests as the Santa Ana Finger Dexterity Test, an arm-hand dexterity test, the Minnesota Rate of Manipulation Test, the Nut and Bolt Assembly Test, the O'Connor Finger Dexterity Test, the Purdue Pegboard, and a modified mirror drawing test with college students. Mild doses (800 mg.) facilitated performance on tasks of intermediate difficulty. Massive doses (1600 mg.) impaired performance on difficult tasks, facilitated it on intermediate tasks, and had no effects on easy tasks.

Margolis and his co-workers confirmed earlier work on the effect of chlorpromazine on Porteus Maze performance. They found that chlorpromazine produced a decrement in maze performance, and that drug effect patterns of schizophrenic outpatients depended on the patient's "level of cognitive development."

A demographic index was shown by Hanlon to increase the precision of a phenothiazine drug research project. He also stated that the index potentially provides a more efficient means of data collection in research requiring measures of severity of illness.

Authors and titles of their papers are listed below.

Barnes, T. C. (Parmae Labs, Dallas, Texas). Further studies of isolation stress in mice and rats.

Barry, Herbert III, and Wagner, Sylvia A. (Yale University, New Haven, Connecticut). Effects of drugs on bar-pressing for food during gradations in fear.

Black, Roger, and Adamson, Robert (Emory University, Emory University, Georgia). The effects of alcohol upon performance in an avoidance-avoidance learning situation.

Blough, Donald S. (Brown University, Providence, Rhode Island). Effects of pentobarbital on discrimination and generalization.

Carlton, P. L. (Squibb Institute for Medical Research, New Brunswick, New Jersey). Some central effects of atropine.

Chambers, Randall M., and Upton, Morgan (Rutgers University, New Brunswick, New Jersey). Effects of a CNS muscle relaxant on performance of finger dexterity tasks of varying difficulty.

Chorover, Stephan L. (New York University-Bellevue Medical Center, New York, New York). Comparison of mescaline- and chlorpromazine-induced impairment of conditional avoidance response (CAR) in the rat.

Clark, Robert, and Polish, Edwin (Walter Reed Army Institute of Research, Washington, D.C.). Effects of avoidance conditioning on alcohol consumption in monkeys.

Davidson, Arnold, Cook, Leonard, and Kelleher, Roger T. (Smith Kline & French Laboratories, Philadelphia, Pennsylvania). The effects of chlorpromazine on performance in a multiple schedule in dogs.

Edwards, R. E., Harris, A. H., and Marlin, R. L. (Sterling-Winthrop Research Institute, Rensselaer, New York). Drug-induced catalepsy and loss of avoidance behavior in rats.

Feldman, Robert S., and Bremner, Frederick J. (University of Massachusetts, Amherst, Massachusetts). The effect of phenelzine on conflict-induced behavior fixations.

Fox, S. S. (University of Michigan, Ann Arbor, Michigan). Sensory deprivation and maintained sensory input in monkeys: behavioral and neuropharmacological studies.

Geller, Irving, and Seifter, Joseph (Wyeth Institute for Medical Research, Philadelphia, Pennsylvania). A new conflict procedure for the evaluation of drugs.

Grossman, S. P. (Yale University, New Haven, Connecticut). Effects of chlorpromazine and Trilafon on bar-pressing in an approach-avoidance conflict.

Hanlon, Thomas E. (Spring Grove State Hospital, Catonsville, Maryland). The use of predictive index in psychiatric drug research.

Heise, George A., Walker, Elizabeth, and Scheckel, Carl (Hoffmann-La Roche, Inc., Nutley, New Jersey). Concurrent measurments of food-reward behavior and stimulation or depressant action of d-amphetamine and other drugs.

Kelleher, Roger T., Fry, William, and Cook, Leonard (Smith Kline & French Laboratories, Philadelphia, Pennsylvania). The effects of chlorpromazine, meprobamate, or phenobarbital on performance on a complex multiple schedule.

Margolis, R., Engelhardt, D. M., Freedman, N., Hankoff, L. D., and Mann, D. (Downstate Medical Center, State University of New York, Brooklyn, New York). Changes in Porteus Maze performance as a function of drug treatment and level of cognitive development.

Mirsky, A. F., and Cardon, P. V., Jr. (National Institute of Mental Health, Bethesda, Maryland). A comparison of the EEG and finger pulse changes accompanying impaired attention following prolonged sleep deprivation and acute chlorpromazine administration.

Myers, Robert D. (Colgate University, Hamilton, New York). The effects of varying alcohol doses on differential lever pressing in the rat.

Otis, L. S., and Berkley, M. A. (Johns Hopkins University, Baltimore, Maryland). Differential effects of psychoactive drugs on components of the water ingestion response in the rat.

Pare, William P. (Boston College, Chestnut Hill, Massachusetts). The effect of caffeine and Seconal on a visual discrimination habit.

Ross, Richard B., and McGaugh, James L. (Carnegie Institute of Technology, Pittsburgh, Pennsylvania, and San Jose State College, San Jose, California). A study of the retroactive effects of strychnine sulphate on maze learning.

Schnitzer, Samuel B., and Ross, Sherman (University of Maryland, College Park, Maryland). The effects of drugs on locomotor behavior.

Schuster, C. R., and Zimmerman, J. (University of Maryland, College Park, Maryland). The effect of chronic administration of dl-amphetamine on timing behavior.

Snapper, Arthur G., Mechner, Francis, and Ray, Ronald (Schering Corporation, Bloomfield, New Jersey). A seven-component multiple schedule for use in human psychopharmacology.

Stein, Larry (Wyeth Institute for Medical Research, Philadelphia, Pennsylvania). Brain-stimulation reward thresholds modified by drugs.

Waller, Patricia F., and Waller, Marcus B. (Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine). The effect of chlorpromazine upon maladaptive behavior in deermice.

Williams, David R., and Miller, Neal E. (Yale University, New Haven, Connecticut). An automation of the potentiated startle technique; and its application to psychopharmacology.

Zimmerman, J., and Schuster, C. R. (University of Maryland, College Park, Maryland). Interaction among components of a multiple DRL schedule.

Western Psychological Association

Howard F. Hunt's Invited Address on "Some Drug-Brain Lesion Interactions and Their Effects upon Behavior" was one of the highlights of the Western Psychological Association meeting held in San Jose, California, in April.

Hunt presented the experiments that he and his colleagues at the University of Chicago have been conducting over the past several years. They have been systematically investigating emotional behavior in animals, with emphasis on conditioned emotional behavior. His report began with a description of work on the effects of drugs on the "savageness" and "irritability" produced in rats when bilateral electrolytic lesions are placed stereotaxically in the septal forebrain. Results of this work led them to study more specifically the problem of the increased responsiveness of septal rats to some, but not all, tranquilizing drugs and to use "sleeping time" as the behavioral indicator of drug effect. In this series of experiments, Hunt and his co-workers have carefully and methodically analyzed the effects of several drugs on septal rats.

In the symposium on "LSD, A Facilitating Agent in Psychotherapy," Ernest Belden of Napa State Hospital (Imola, California) presented a brief historical review of LSD from the time of its discovery by Hofmann to its present experimental use in psychotherapy. He mentioned that he thought that LSD has a specific drug effect, not necessarily related directly to the psychodynamics of the subject or patient. A description of procedures and techniques to be followed in administering LSD in the psychotherapeutic situation was given by Betty G. Eisner of Los Angeles. Joe K. Adams of the Mental Research Institute felt that LSD is useful as a phenomenological approach to the study of general psychology. Loriene Johnston of Los Angeles presented a case of a therapy session with LSD, and Wilson Van Dusen of Mendocino State Hospital (Talmage, California) analyzed the subjective LSD experience. Jack Blumenkrantz of the Veterans Administration Hospital in San Francisco, California, discussed the papers in the role of a friendly skeptic. He agreed that LSD has been demonstrated to be a potent drug but raised questions about some of the explanations of its effects.

Other work relevant to psychopharmacology was presented in a symposium on "Relations between Learning and Brain Chemistry in the Rat," chaired by David Krech of the University of California, Berkeley, and in the following papers:

Karoly, Andrew J. (Humboldt State College, Arcata, California). Behavioral tests of rats under chronic reserpine.

Rosman, Richard R. (University of Illinois, Chicago, Illinois). Relations between effects of two psychotropic drugs on the apparent horizon and mood.

Tyson, R., Young, S., and Haralson, J. V. (Los Angeles State College, Los Angeles, California). The effect of reserpine on a conditioned and an unconditioned operant in fish (Tilapia mozambica).

Westbrook, William, McGaugh, James L., and Ross, Richard (San Jose State College, San Jose, California.) Retroactive effects of 5-7 diphenyl-1-3-diazadamantan-6-OL (1757I.S.) on maze learning and retention.

Research Conference on Patterns of Transition from Hospital to Community

The importance of preventing relapse and improving the level of adjustment and personal functioning of patients discharged from mental hospitals was sharply emphasized at the three-day Research Conference on Patterns of Transition from Hospital to Community, held in Boston in March. Recognizing that problems related to relapse and rehospitalization will increase as hospital discharge rates increase, an informal group of investigators organized this conference to focus attention on the need for continued treatment of discharged patients and to review and discuss methods and techniques of treating patients in their homes and communities.

This was the third in a series of conferences organized by a group of psychiatrists, psychologists, social workers, and sociologists interested in research on psychiatric treatment. The first, held in Montreal in 1958, was concerned with the dynamics of psychiatric drug therapy. The second, held in New York in 1959, was devoted to papers and discussions on the therapeutic community. The proceedings of these conferences—the first edited by G. J. Sarwer-Foner, the second by Herman C. B. Denber—have been published by Charles C Thomas of Springfield, Illinois. The proceedings of the Boston conference will also be published and will be edited by Milton Greenblatt (Massachusetts Mental Health Center), Daniel J. Levinson (Massachusetts Mental Health Center), and Gerald L. Klerman (Psychopharmacology Service Center), who served as the conference planning committee.

Although a good deal of attention was given to the role of drug therapy, the emphasis on the conference was on the psychiatric patient's successful transition from hospital to community. Several different types of hospital after-care facilities were described. A number of papers dealt with the importance of community and family attitudes toward discharged patients. Others reported follow-up studies, controlled evaluations of maintenance drug therapy, studies of the comparative efficacy of different types of treatment, or dealt with the need for evaluating the effectiveness of methods and techniques which are being used in this area.

Discharge Planning and Transitional Facilities

Problems of discharge planning were considered in the first session, which was in large part dominated by discussion of the concept of institutional dependency. Gralnick outlined the hospital's role in promoting dependency, pointing out that dependency is an inevitable consequence of hospitalization, but emphasizing that it has positive as well as negative therapeutic aspects. Lipsett's paper, also on dependency, reported a study in which it was found that long-term patients denied their dependency needs to a significantly greater degree than did short-term or voluntarily committed patients. The discussion following these presentations highlighted the need for continued study and clarification of the concept of institutional dependency, its relation to dependency in general, and its role in promoting or retarding the progress of treatment.

Mrs. Lyman and several other participants described various aspects of Rutland Corner House, a residential unit or "halfway house" for female patients released from the Massachusetts Mental Health Center. Their papers covered the history of the clinic, its selec-

tion practices, and the present program of sociological research. Wechsler gave a report and demonstration on the role of social therapy clubs. The paper by Boag described the day- and night-hospitals which have been functioning successfully in Montreal for a number of years.

Katz's paper stressed the need for evaluation of the effectiveness of transitional facilities. Although he recognized the difficulties inherent in this kind of research, he emphasized that many of the problems are quite similar to those encountered in the evaluation of psychiatric treatment generally. He observed that a number of methodological advances have stemmed from investigations of drug therapy. As examples, he pointed to new methods of diagnostic classification and new methods of evaluating paitent change. These and other new techniques, he felt, could be used in studies of the effectiveness of transitional facilities, and he asked researchers to take advantage of them.

Community and Family Influence and Support

The session on community influences and supports was opened by Brooks, who singled out good hospital-community relations as a key factor in the adjustment of formerly hospitalized patients. He observed that the quality of the contact between hospital and community was crucially important, and that mere establishment of contact was in itself inadequate. He drew attention to the many services which discharged patients could provide in the community, and suggested that patient service to the community could play a significant role in improving community attitudes toward the mentally ill.

Rajotte and Denber, reporting an intensive follow-up study of chronic psychotics with a history of relapse, found that maintenance drug therapy plus continued contact with a community treatment facility were the important factors in preventing relapse. They reported that relapse rate dropped markedly when continuity of contact was maintained and drug therapy was integrated into the total treatment program.

Preliminary findings reported by Kris tended to confirm the findings presented by Rajotte and Denber. She described a project, still under way, comparing two methods of treating relapsed patients. The patients are described on a psychopathology scale and then randomly assigned to the two treatment groups: one group is rehospitalized and the other is treated with drugs in a day-care center. Following recovery, the community adjustment of the two groups will be evaluated. Although the findings are still preliminary, the results of day care plus drug have thus far been very encouraging; almost all patients in this group have returned to the community within six weeks. At the time of the conference, the progress of the rehospitalized patients had not been evaluated, but Kris stated that such patients would be closely followed up after their discharge from the hospital.

Family influences on patients' adjustment were discussed in a number of papers. Simmons summarized a five-year program of investigation of the social, personal, family, and community factors associated with the rehospitalization of discharged patients and briefly described plans for following up the findings and the major hypotheses derived from the program. Grinspoon, Courtney, and Bergen presented a demonstration of the use of group techniques with patients' parents.

The Role of Pharmacotherapy

The session on pharmacotherapy included a review, by Klerman, of the historical background against which the results of maintenance drug therapy of discharged patients could be evaluated. He noted that discharge rates for schizophrenia and functional psychoses had been increasing for many years. In the 1930's and 1940's, the discharge rate of newly admitted patients began to rise; by the early 1950's, even before the tranquilizers were widely used, more than 50 per cent of newly admitted patients at intensive treatment centers were being discharged. The introduction of drug therapy accelerated this trend and has enabled most hospitals to intensify their treatment programs. Klerman observed, however, that although previous therapies had increased the proportions of acute patients being discharged,

none had improved the rehospitalization rate; the social adjustment of many discharged patients was often only marginal and their long-term outlook seemed poor. Only since the introduction of drug therapy have after-care programs given promise of altering this picture.

Freyhan and Merkel described a home-treatment program which the Delaware State Hospital has been conducting for several years. Many patients discharged from the hospital are now in the community on compensatory drug treatment. They are visited regularly in their homes by a public health nurse who supervises their drug therapy and observes social and family processes. Specific psychopathological symptoms, rather than global diagnostic classification, are used as indications for drug therapy. The high relapse rate in a small group of patients switched from drug to placebo has reinforced the clinical impression that drug therapy is necessary as long as the patient has signs or symptoms of psychopathology.

Gross reported similar findings from a double-blind study of more than 100 chronic psychotics continued on tranquilizers after their release from Springfield (Maryland) State Hospital. After the patients had been on drug therapy for at least five months following discharge and after their clinical picture had stabilized, they were randomly assigned to either a control group and continued on active medication, or to an experimental group and gradually withdrawn from active medication until placebo only was being given. The relapse rate among the experimental group was found to be many times higher than among the control group. The investigators noted that the conclusions drawn from this study were particularly applicable to patients who had psychoses of long duration. They cautioned that patients should be followed for at least one year after cessation of drug therapy.

A third paper reporting relapse in patients switched from drug to placebo was presented by Wold. For over two years she closely observed a group of six chronic schizophrenics who were being maintained on chlorpromazine after discharge from a state hospital. Each patient was switched from chlorpromazine to placebo on at least two occasions. Five of the six patients relapsed both times. The time of relapse varied from a few days to a number of months after chlorpromazine was stopped. Wold observed that each of the five patients who relapsed showed a characteristic pattern, both as to time of recurrence of symptoms and as to the symptom picture manifested.

Engelhardt and Freedman described a special research clinic in Brooklyn and reported a study of ambulatory schizophrenics who were randomly assigned to treatment with chlorpromazine, promazine, or placebo. The progress of the patients was assessed by psychiatric ratings; social adjustment was determined by tests and special interviews with relatives. In this study, chlorpromazine proved to be superior to the other medications in preventing hospitalization, improving pathological thought processes, and facilitating social adjustment.

Many investigators agreed that long-term drug therapy is feasible and efficacious, and that some of the phenothiazines are particularly suitable for long-term administration, especially in view of the fact that maintenance doses are usually much lower than doses used for the control of active psychotic symptoms. Although side effects such as drowsiness, lethargy, lactation, menstrual irregularities, and weight gain occasionally occur, it was reported that these symptoms could usually be managed by a reduction in dosage. Several investigators, including Brooks and Freyhan, reported the development of a mild "withdrawal syndrome" manifested by insomnia, irritability, malaise, and incoordination when phenothiazine medications were stopped abruptly, but they observed that these symptoms did not occur when the drug was stopped gradually. Liver and blood complications were reported to be extremely rare after the first months of treatment with phenothiazine derivatives.

The conference seemed to substantiate the need for prolonged drug therapy of chronic psychotics, but the role of long-term drug therapy for patients recovering from acute psychotic illnesses was less clear.

Authors and Titles of Papers

Listed below are the authors and titles of papers presented at the conference. These

papers will be published in the conference proceedings.

Boag, T. J. (Allan Memorial Institute of Psychiatry, Montreal, Canada). Day and night hospital as center of hospital-community activities.

Brooks, George W. (Vermont State Hospital, Waterbury, Vermont). Rural community influences and supports in a rehabilitation program for state hospital patients.

Engelhardt, David. (State University of New York, Downstate Medical Center, Brooklyn, N. Y.) Role of pharmacotherapeutic agents in treatment of schizophrenic out-patients.

Freyhan, F. A., and Merkel, Joan (Delaware State Hospital, Farnhurst, Delaware). Clinical and social aspects of compensatory drug treatment in psychiatric patients.

Gomness, Claire (Rutland Corner House, Boston, Massachusetts). Halfway House—a clinic; supervision.

Gralnick, Alexander (High Point Hospital, Port Chester, New York). Problems of the patient in transit from hospital to community.

Grinspoon, Lester, Courtney, Phyllis H., and Bergen, Helen M. (Massachusetts Mental Health Center, Boston Massachusetts). Group therapy with parents of patients: a demonstration.

Gross, Martin (Springfield State Hospital, Sykesville, Maryland). Withdrawal of ataractic drugs in asymptomatic psychotic patients: a controlled study.

Kaplan, Stanley M., and Curtis, George C. (University of Cincinnati and Cincinnati General Hospital, Cincinnati, Ohio). Reactions of medical patients to discharge or threat of discharge from a psychosomatic unit of a general hospital.

Katz, Martin M. (Psychopharmacology Service Center). Problems in evaluation of effectiveness of transitional facilities.

Klerman, Gerald L., and Cole, Jonathan O. (Psychopharmacology Service Center). Base lines for the evaluation of maintenance therapy.

Kris, Else B. (New York State Department of Mental Hygiene, New York, New York). Prevention of rehospitalization through relapse control in a day hospital.

Landy, David (Massachusetts Mental Health Center, Boston Massachusetts). Halfway House —a clinic; social science viewpoint.

Lipsitt, Don R. (St. Elizabeths Hospital, Washington, D. C.). Institutional dependency: a rehabilitation problem.

Lurie, Abraham, and Pinsky, Louise (Hillside Hospital, Glen Oaks, New York). Role of community agencies in post-hospital planning of psychiatric patients.

Lyman, Mrs. Ronald T., Jr. (Rutland Corner House, Boston, Massachusetts). Halfway House —a clinic; history and organization.

Meszaros, A. F., and Meszaros, E. S. (Ste. Annes Veterans Hospital, Ste. Anne de Bellevue, Canada). Integration of the discharged schizophrenic patient within the family.

Ogilby, Anne P., and Greenblatt, Milton (Massachusetts Mental Health Center, Boston, Massachusetts). Halfway House—a clinic; patient demonstrations.

Ogle, William A. (Seattle, Washington). Report on experiences of psychiatrists working with general practitioners on post-psychiatric hospital care.

Rajotte, Paul, and Denber, Herman C.B. (Manhattan State Hospital, Ward's Island, New York). Intensive follow-up study of sixty chronic relapsing psychotic female patients.

Rapoport, Rhona V. (Harvard School of Public Health, Boston, Massachusetts). The patient's family: asset and liability.

Silver, A., Wilner, S., and Sarwer-Foner, G. J. (Jewish General Hospital, Montreal, Canada). The problems of discharge planning for patients in a psychiatric unit of a general hospital.

Simmons, Ozzie G. (Harvard School of Public Health, Boston, Massachusetts). After hospitalization: the mental patient and his family.

Wechsler, Henry (Massachusetts Mental Health Center, Boston, Massachusetts). The ex-patient club: a general survey and case study.

Wold, Patricia N. (Arlington, Massachusetts). Long-term study of chlorpromazine in six chronic schizophrenic patients.

American Psychiatric Association

Psychopharmacological papers presented at the American Psychiatric Association annual meeting in Atlantic City, held in May, were quite varied in content. One of the liveliest and most interesting was Bowes and Gilbert's report on the treatment of depression in outpatients seen at the Northeast South Dakota Mental Health Center in Aberdeen, South Dakota. The Center, established less than two years ago, provides outpatient psychiatric treatment for a widely scattered population in an agricultural region. Despite the infrequency of visits to the Center—many of the patients live some distance away—the results of treatment have thus far been very encouraging and untoward side effects very infrequent.

When the Center first opened, drugs and psychotherapy were the only treatments used, and hospital facilities for psychiatric patients were not available. Later, when arrangements were made to admit Center patients to the local general hospital, electroshock therapy could be used. Bowes reported that of the first 100 depressed patients treated at the Center, 85 recovered or improved markedly on pharmacotherapy plus supportive psychotherapy; 12 were hospitalized for periods not exceeding six days and were given electroshock therapy in addition to drugs; and only 3 were sent to mental hospitals. No suicides occurred. Chlorpromazine or methaminodiazepoxide administered in combination with antidepressive medication was found helpful in allaying anxiety during the period before the antidepressive became effective.

Experiences with drug therapy in the treatment of depression in outpatients were also reviewed by Furst, who was one of the participants in a round-table meeting on "Methods of Administration, Dosage and Side Effect Control of Phrenopraxic Drugs." He felt that iproniazid was perhaps the best drug, but noted that phenelzine also seemed promising.

At the same session, Denber described a clinical trial with thioperazine (RP-7843), a phenothiazine derivative with a sulfanilamide group in the two position. In intramuscular doses of 1 to 5 mg. t.i.d., followed by oral doses of 20 to 30 mg. t.i.d., the drug seemed to be a potent agent for the treatment of chronic schizophrenia. It caused a high incidence of extrapyramidal effects, but these symptoms were easily controlled by the use of procyclidine.

Other round-table participants included Cazzulo, who presented some interesting neuroanatomical slides depicting nerve-cell changes in response to various drugs and who also discussed the use of imipramine in the University of Milan Psychiatric Clinic; Sarwer-Foner, who reported a study of trifluprομazine and discussed the complex interaction between the pharmacological effects of drugs and the psychodynamic meaning of the effects to the patient; Goldman, who reported a trial of fluphenazine; and Freyhan, who classified the phenothiazine derivatives by chemical structure and type of activity. He expressed the view that the phenothiazines that have a high incidence of extrapyramidal side effects are more effective in hypokinetic patients, whereas chlorpromazine is more effective in hyperkinetic patients.

Tobin was scheduled as a participant but was unable to attend. His report on a study of methaminodiazepoxide (Librium) was presented by a colleague. Data collected by a group of private practitioners were pooled and analyzed centrally by Tobin. Psychiatrists' ratings and patients' self-ratings of improvement of anxiety were made. Eighty-seven per cent of the patients and 80 per cent of the psychiatrists noted slight to marked improvement after treatment with divided daily doses of 40 to 175 mg. Since many of the patients had failed to respond to other mild tranquilizers, these psychiatrists felt that methaminodiazepoxide showed definite advantages over other drugs as a treatment for anxiety in outpatients. It was noted that ataxia and drowsiness were encountered with the higher doses, and that older patients seemed to be particularly susceptible to these side effects.

In a session of papers on chemotherapy, Fort reported on the use of drugs as an adjunct to the long-term psychotherapy of chronic schizophrenics at Chestnut Lodge. Although some of the patients did quite well on drugs, others showed undesirable effects, and in some cases it was felt that the addition of drug therapy had been detrimental to progress in psychotherapy. Throughout his paper, Fort stressed the doctor-patient relationship as an important factor in the usefulness or success of drug therapy.

A second paper concerned with drugs plus psychotherapy was the one presented by Eisenberg et al., who described an investigation of the effects of psychotherapy alone, psychotherapy plus placebo, and psychotherapy plus perphenazine in the treatment of hyperkinetic or neurotic children. In the hyperkinetic children, but not in the neurotic, psychotherapy plus perphenazine appeared to be more effective than either of the other two treatments. Although this trend was not statistically significant, it was accentuated by the additional observation that the hyperkinetic children became worse when perphenazine was discontinued. In the neurotic children, psychotherapy plus placebo was no more effective than psychotherapy alone. Their improvement rates, irrespective of method of treatment, were much higher than those of the hyperkinetic children.

Other papers relevant to psychopharmacology were scattered throughout the meeting. One, by Furst and Furst, explored some of the ethical and legal aspects of drug research. Several (Moore and Spivak, Rashkis, and McCreight et al.) dealt with some of the complications and complexities of conducting clinical research in a treatment-oriented hospital, discussing the relations between clinical and research staffs, the effect of research on over-all goals and activities of the hospital, and possible solutions to some of the administrative and procedural difficulties which arise.

Bennett and Kooi's paper described a double-blind investigation of the toxic effects of five phenothiazine derivatives in a group of 30 schizophrenics. In six weeks, a peak daily dosage equivalent to 1200 mg. of chlorpromazine was reached; dosage was continued at that level through the 13th week in all but two patients, both of whom developed severe parkinsonism. Among other findings, it was reported that this dosage schedule induced cerebral dysfunction suggestive of both basal and cortical involvement, and that a high correlation existed between clinical remission and induced cerebral dysfunction.

The authors and titles of these and other psychopharmacological papers presented at the meeting are listed below:

Abse, D. Wilfred, and Dahlstrom, W. Grant (University of North Carolina, Chapel Hill, North Carolina). A controlled comparison of chemotherapy with chlorpromazine, reserpine-Meratran and opium in senile mental disturbances.

Alexander, Leo (Tufts University Medical School, Boston, Massachusetts), and Lipsett, Suzanne R. (Boston State Hospital, Boston, Massachusetts). The effect of drugs on the conditional psychogalvanic reflex in man.

Bennett, Jesse L., and Kooi, Kenneth A. (Veterans Administration Hospital, Salt Lake City, Utah.) Evaluation and toxicity studies of five phenothiazine derivatives.

Bogoch, Samuel, Dussick, Karl T., Fender, Christa, and Conran, Peter, (Harvard Medical School, Boston, Massachusetts). Longitudinal clinical and neurochemical studies on schizophrenic and manic-depressive disorders.

Bowes, H., Angus, and Gilbert, James E. (Northeast South Dakota Mental Health Center, Aberdeen, South Dakota). The anti-depressant drugs in an out-patient setting.

Caffey, Eugene M., Jr. (Veterans Administration Hospital, Perry Point, Maryland). Experiences with large scale interhospital cooperative research in chemotherapy (the VA cooperative chemotherapy studies in psychiatry).

Cazzullo, C. L. (Clinica Psichiatrica, Universita degle Studi di Milano, Milan, Italy). Participant in the round-table meeting on "Methods of Administration, Dosage and Side-Effect Control of Phrenopraxic Drugs."

Cole, Nyla J., Allison, Roger B., and Branch, C. H. Hardin (University of Utah, Salt Lake City, Utah). Studies of behavior and the metabolism of indole derivatives in schizophrenia.

Denber, Herman C. B. (Manhattan State Hospital, New York, New York). Participant in the round-table meeting on "Methods of Administration, Dosage and Side-Effect Control of Phrenopraxic Drugs."

Eisenberg, Leon, Gilbert, Anita, Molling, Peter, and Cytryn, Leon (Johns Hopkins Hospital,

Baltimore, Maryland). The effectiveness of psychotherapy alone and in conjunction with perphenazine or placebo in the treatment of neurotic and hyperkinetic children.

Esecover, Harold, Malitz, Sidney, and Wilkens, Bernard (New York State Psychiatric Institute, New York, New York). Clinical profiles of paid normal subjects volunteering for hallucinogenic drug studies.

Fort, John P. (Chestnut Lodge, Rockville, Maryland). Long-term psychotherapy of schizophrenic patients in conjunction with drug use.

Freyhan, Fritz (Delaware State Hospital, Farnhurst, Delaware). Participant in the round-table meeting on "Methods of Administration, Dosage and Side-Effect Control of Phrenopraxic Drugs."

Froham, Charles E., Luby, Elliot D., Tourney, Garfield, Beckett, Peter G. S., and Gottlieb, Jacques S. (Lafayette Clinic, Detroit, Michigan). Steps toward the isolation of a serum factor in schizophrenia.

Furst, William, and Furst, William (East Orange, New Jersey). Medical, pharmaceutical and legal responsibility in psychiatric research.

Goldman, Douglas (Longview State Hospital, Cincinnati, Ohio). Participant in round-table meeting on "Methods of Administration, Dosage and Side-Effect Control of Phrenopraxic Drugs."

Heath, Robert Galbraith, Verster, Floris deBalbian, Byers, Lawrence Wallace, and Leach, Byron Elwood (Tulane University, New Orleans, Louisiana). Effects of chemical stimulation to discrete brain areas.

McCreight, David W. (New Jersey State Hospital, Marlboro, New Jersey), Lewis, Nolan D. C., and Tobin, Joseph M. (New Jersey Neuro-Psychiatric Institute, Princeton, New Jersey). A research model for the evaluation of the effect of psychopharmacological agents.

Moore, Kenneth B., and Spivak, Mark (Ypsilanti State Hospital, Ypsilanti, Michigan). The establishment of a multidisciplinary research program within the state mental hospital.

Nielsen, Donald R., and Selbst, Ronald A. (University of Michigan Neuropsychiatric Institute, Detroit, Michigan), and Rosenzweig, Norman (University of Michigan, Ann Arbor, Michigan). Meprobamate-benactyzine in the treatment of depression in outpatients.

Rashkis, Harold A. (Eastern Pennsylvania Psychiatric Institute, Philadelphia, Pennsylvania). Does clinical research interfere with treatment?

Rose, Milton, and Esser, Mary Ann (Stanford University, San Francisco, California). The impact of recent research developments on private practice.

Sarwer-Foner, G. (McGill University, Montreal, Canada). Participant in the round-table meeting on "Methods of Administration, Dosage and Side-Effect Control of Phrenopraxic Drugs."

Tobin, Joseph (New Jersey Neuro-Psychiatric Institute, Princeton, New Jersey). Scheduled as participant in round-table meeting on "Methods of Administration, Dosage and Side-Effect Control of Phrenopraxic Drugs."

American Society of Medical Psychiatry

The second annual meeting of the American Society of Medical Psychiatry was held in Atlantic City on May 8 prior to the American Psychiatric Association meeting. A number of papers concerned with the biochemistry or pharmacotherapy of mental illness were presented.

Rothman et al. reported a controlled comparison of isocarboxazid and imipramine in depressive syndromes. Although both drugs were useful and effective, they seemed to have different modes of action. The patients on isocarboxazid showed a more definite mood elevation, almost a frank euphoria in some cases. Imipramine also reduced the effects of the depression, but it did not cause the change in psychomotor activity seen in the patients receiving isocarboxazid. The clinical implications of the findings were discussed. Extensive physiological measures were also made during the study but were not reported at this meeting.

Coirault's paper reported clinical experience with a new French compound, A.N.P. 235, which has been described as a promising new therapeutic agent for the treatment of both psychiatric and general medical disorders. This compound, which is the dimethylaminoethyl ester of parachlorophenoxy acetic acid, not only seemed to control agitation and anxiety, but also appeared to make patients more "lucid." Using the drug in the treatment of a wide range of clinical syndromes, Coirault found it to be very effective in many patients.

A study of another French compound, S.C.T.Z.–4-methyl-5(β-chloroethyl)-thiazole ethanedisulfonate–was described in the paper by Singh. It was reported that intravenous administration produced sleep of rapid onset and short duration in a number of agitated and restless patients. The effects were enhanced when the drug was combined with electroshock or chlorpromazine. A disadvantage, however, was the incidence of phlebitis following intravenous administration of the drug.

The results of a pilot study of "serum normalizing therapy" were reported by LaVerne. Pooled human serum and cerebrospinal fluid were administered intradermally to a group of 50 psychiatric patients refractory to usual therapies. After a series of weekly serum injections, clinical improvement was observed in several diagnostic groups. The serum was considered to have a "nonspecific action" of unknown mechanism. In a number of patients, the magnitude of the skin reaction seemed to be correlated with clinical response. Hyperreactive patients had a hypersensitive skin reaction and hyporeactive patients showed hyporeactive skin reactions to intradermal injections of serum. LaVerne felt that the results of this therapy, though not conclusive, were worthy of further study.

Follow-up data on the use of pooled normal blood injections in chronic schizophrenics were presented by Weiss and LaVerne. The injections proved to be superior to saline placebo in this group of patients, but 7 to 12 months of treatment were required before improvement was noted.

Moriarty discussed the interaction of drugs and psychotherapy, noting that the combination was often appropriate and advantageous to both patient and therapist. Drug may make the patient more accessible to psychotherapy and perhaps shorten the time needed for therapy, but Moriarty observed that these advantages could be offset by the possibility of drug dependence or by covering up problems rather than resolving them.

Kraines presented a theoretical model to explain drug action. He described an "emotional circuit" comprising various levels of the nervous system, and discussed drug actions in terms of the levels at which they operate.

Geiger reported a study in which C^{14}-labeled glucose was used to locate areas of turnover of labeled products in the brain after periods of stress or learning. Using rats as subjects, he found that changes in areas of greater turnover were related to changes in the composition of nucleic acids after brain stimulation. He suggested that changes in nucleic acids may be the physiological correlate of memory.

Liberson and Ellen reported an investigation of the effects of various monoamine oxidase (MAO) inhibitors and of LSD-25 on behavioral fixations and operant behavior of rats, in a situation in which a reward was given for responses to only one of the two windows in the apparatus. The MAO inhibitors improved responses (decreased latency) to the rewarding window but had little effect on responses to the unrewarding window. LSD had a generally disruptive effect on behavior in these situations.

Listed below are the authors and titles of these papers:

Coirault, R. (Clinique Neuro-Psychiatrique, Paris, France). L'ester dimetyl amino ethylique de l'acide parachloro phenoxy-acetique.

Geiger, Alexander. (University of Illinois, Chicago, Illinois). Selected aspects of brain metabolism and function.

Kraines, S. H. (Chicago, Illinois). Psychotropic drugs and the emotional circuit.

LaVerne, Albert A. (Bellevue Psychiatric Hospital, New York, New York). Serum normalizing therapy.

Liberson, W. T., and Ellen, Paul. (Veterans Administration Hospital, Hines, Illinois). Further studies of the influence of psychotropic drugs on behavior of rats.

Moriarty, John D. (Los Angeles, California). Drug therapy versus psychotherapy.

Rothman, Theodore, and Ferguson, James. (Veterans Administration Center, Los Angeles, California). A comparative investigation of isocarboxazid (Marplan) and imipramine (Tofranil) in depressive syndromes.

Singh, Kirpal. (Military Hospital, Poona, India). Clinical uses of S.C.T.Z.—a preliminary report.

Weiss, Deso A. (Creedmoor State Hospital, Queens Village, New York), and LaVerne, A. A. (Bellevue Psychiatric Hospital, New York, New York). Follow-up of the Creedmoor study using the biochemical hemo-extract.

Society of Biological Psychiatry

At the meeting of the Society of Biological Psychiatry, held in Miami on June 10, 11, and 12, encouraging results of follow-up studies of discharged psychiatric patients were presented in three papers, one by Kris of the Manhattan After-Care Clinic, a second by Tuteur et al. from Elgin (Illinois) State Hospital, and the third by Gross and co-workers from Springfield (Maryland) State Hospital. In all three, pharmacotherapy appeared to play a crucial part in the prevention of rehospitalization. The group from Illinois reported a return rate of only 26 per cent among a group of patients maintained on chlorpromazine following discharge, as contrasted with the 40 per cent over-all return rate at this hospital, and a 60 per cent relapse rate in a control group of patients who were placed on placebo after discharge from the hospital.

The study reported by Gross et al. revealed a much higher relapse and rehospitalization rate among discharged patients who were switched to placebo than among those who were maintained on drug. These workers suggested that patients be kept on drug therapy for at least two years following discharge from a hospital.

Kris, too, stressed the importance of continuing medication. Her five-year follow-up study not only revealed a lower relapse rate among patients on maintenance drug therapy, but also showed that drug therapy did not interfere with the patients' performance on the job or in school.

Studies of the effects of serotonin and 5-hydroxtryptophan (5-HTP) on learned behavior in animals were presented by Birk et al. and by Aprison and Ferster. Using dogs as subjects, Birk et al. found that serotonin was less effective than 5-HTP in blocking conditioned responses, but Aprison and Ferster reported opposite results in pigeons. Although their results showed that 5-HTP disrupted performance, they found that a comparable disruption of performance could be produced by smaller amounts of serotonin than of 5-HTP.

Harold and Williamina Himwich and their co-workers reported further investigations of the effects of intracarotid and intravertebral arterial injections of serotonin analogues. They found that two isomers of methyltryptamine—both amine oxidase inhibitors—evoked an EEG arousal pattern when injected in the posterior cerebral circulation but not when injected in the anterior cerebral circulation. Injection of 5-HTP in dogs pretreated with an MAO inhibitor (SKF 385) impaired motor integration to various degrees and caused neurovegetative and behavioral changes. On the basis of behavioral analyses of the effects of 5-HTP injected into the carotid or vertebral circulation of normal dogs and dogs whose basilar artery had been clipped, these investigators concluded that maximal effects occur when the excess serotonin is formed in midbrain areas.

A study of the effects of chlorpromazine, trifluoperazine, perphenazine, and promethazine on psychological, psychomotor, physiological, and emotional parameters of "normal" human subjects was reported in the paper by DiMascio, Snell, and Havens. Each of the four drugs presented a different "psychophysiological profile." There was, however, some ques-

tion about whether the profiles could be used as predictors of the clinical usefulness of the drugs, or whether they merely differentiated the drugs on the basis of differences in side effects.

Silva and co-authors compared the effects of taraxein, LSD, and mescaline, which were administered separately to four human volunteers. Of the symptoms caused by the three drugs, those produced by taraxein were reported to be more characteristic of the symptoms of schizophrenia, and fewer nonspecific toxic symptoms were caused by taraxein than by the other two drugs.

The effects of laboratory and "real-life" stress on catechol amines in human subjects were described in a paper by Silverman et al. The findings suggested altered adrenalin-noradrenalin ratios in different affect states. Adrenalin levels were higher in anxious subjects, whereas noradrenalin was higher in the angry ones.

Marrazzi discussed a potential histaminogenic mechanism for psychosis. By introducing minute amounts of histamine into the cerebral circulation of the cat, Marrazzi and co-workers, Hart and Gilfoil, duplicated the impediment to cerebral synaptic transmission produced by exogenous psychotogens such as LSD. Antihistamines counteracted the effect.

Especially noteworthy was an excellent review, by Marrazzi and Himwich, of the theories of the mode of action of psychopharmacological agents.

Listed below are the authors and titles of the papers that were most directly relevant to the field of psychopharmacology:

Aprison, M. H., and Ferster, C. B. (Indiana University, Indianapolis, Indiana). Serotonin and behavior.

Azima, H. and Vispo, R. H. (Allan Memorial Institute, Montreal, Canada). Drug induced anaclitic situation.

Birk, C. L., Conti, L., and Gantt, W. H. (Johns Hopkins University, Baltimore, Maryland). Action of serotonin on higher nervous activity.

DiMascio, A., Snell, J., and Havens, L. (Massachusetts Mental Health Center, Boston, Massachusetts). "Psychophysiological profiles" of 4 phenothiazine derivatives.

Gross, Martin, Hitchman, Irene L., Reeves, Walter P., Lawrence, Jordan, and Newell, Pauline C. (Springfield State Hospital, Sykesville, Maryland). Discontinuation of treatment with ataractic drugs.

Heath, Robert G., Ehrensvard, Gosta, Leach, Byron E., and Johnson, Richard (Tulane University, New Orleans, Louisiana). Studies of biochemical differences in specific brain tissues of rhesus monkeys under normal conditions and under the influence of taraxein.

Himwich, Harold E., Costa, Erminio, Ayala, Giovanni, and Van Meter, William G. (Galesburg State Hospital, Galesburg, Illinois). The effects of intravertebral and intracarotid administration of methyl tryptamine on the electrical activity of the rabbit brain.

Himwich, Williamina A., Costa, Erminio, and Himwich, Harold E. (Galesburg State Hospital, Galesburg, Illinois). Action of 5-hydroxytryptophan on selected arterial sites in the brain.

Kris, Else B. (New York State Department of Mental Hygiene, New York, New York). Effects of pharmacotherapy on work and learning ability. A five year follow-up study.

Marrazzi, Amedeo S., Hart, E. Ross, and Gilfoil, Thomas M. (Veterans Administration Hospital, Pittsburgh, Pennsylvania). A potential histaminogenic (allergic?) mechanism for psychosis.

Marrazzi, A. (Veterans Administration Hospital, Pittsburgh, Pennsylvania), and Himwich, H. E. (Galesburg State Hospital, Galesburg, Illinois). Review paper—theories on the mode of action of psychopharmacological agents.

Silva, Francisco, Heath, Robert G., Rafferty, Thomas L., and Leach, Byron E. (Tulane University, New Orleans, Louisiana). Comparative effects of taraxein, LSD and mescaline.

Silverman, A. J., Cohen, S. E., Shmavonian, B. M., and Kirshner, N. (Duke University,

Durham, North Carolina). Catechol amines in psychophysiologic studies.
Tuteur, Werner, Stiller, Rochus, and Glotzer, Jacob (Elgin State Hospital, Elgin, Illinois). Chlorpromazine–five years later.

American Medical Association

A panel discussion on psychopharmacology was jointly sponsored by the Section on Nervous and Mental Diseases and the Section on Experimental Medicine and Therapeutics of the American Medical Association at the annual meeting of the AMA, held in Miami, Florida, June 13-17. Panelists were Leo E. Hollister (Veterans Administration Hospital, Palo Alto, California), Fritz A. Freyhan (Delaware State Hospital, Farnhurst, Delaware), Jonathan O. Cole (Psychopharmacology Service Center, NIMH, Bethesda, Maryland), and S. Bernard Wortis (New York University, New York, New York). Samuel P. Martin (University of Florida, Gainesville, Florida) served as moderator.

Freyhan stressed the importance of the symptom complex in individual patients and emphasized the necessity of treating target symptoms rather than diagnostic groups. Discussing the role of dyskinetic symptoms in relation to drug action, he emphasized that drug therapy should be viewed as a treatment of major import, not one to be used lightly or without proper care, caution, and indications.

Wortis gave the audience four main points to remember: (1) It is a poor habit to prescribe drugs for every case of slight emotional tension. (2) Drugs are not an adequate substitute for proper mental, physical, or social adjustment. (3) Drugs alone are not curative; they should be used only in conjunction with other methods of therapy. (4) It is better for the prescribing physician to concentrate on the use of one particular drug in a given class than to switch from one drug to another as new ones appear on the market.

Hollister reviewed the important side effects of the drugs commonly used in psychiatry. Drawing special attention to the importance of close and careful clinical observation in detecting hepatic and hematopoietic complications, he warned against relying solely on routine laboratory tests. Although treatment should be prompt and vigorous when complications do occur, he emphasized that no attempt should be made to treat possible complications before they appear. The latter approach, he noted, leads to "polypharmacy."

Cole's remarks were directed primarily towards the importance of–and the scarcity of–carefully controlled clinical studies of drugs. He also discussed the growing interest in evaluations of the interaction between drug and the doctor–patient relationship.

From the floor, the danger of using many antidepressive agents in the same patient was mentioned. It was noted that the use of imipramine should be avoided immediately after stopping administration of a hydrazine derivative.

A. Friedhoff (New York University, New York, New York), also speaking from the floor, presented data on the dangers of inadequate dosage. He observed that serious side effects can occur on doses which are too low to produce clinical improvement.

Additional psychopharmacological studies were reported in other sessions of the meeting. Among them was the paper by Arthur S. Keats, Jane Telford, and Yoshio Kurosu of Houston, Texas, who reported that they found that–contrary to the usual opinion–the analgesic, respiratory, and sedative effects of meperidine are not potentiated, in man, by promethazine. They stated that it had been difficult to demonstrate even additive effects.

Sidney Cohen and Ruth M. Pillsbury, of Los Angeles, California, reported on the prolonged use of high doses of thioridazine in the treatment of deteriorated, regressed, chronic schizophrenics. The drug mobilized sufficient numbers of patients, who began to relate and participate in ward activities, so that the entire ward atmosphere changed. Despite the high dosage levels there was a low incidence of side effects.

Workshop on Drug Therapy for Children*

A workshop on "Use of Drug Therapy for Children as part of a Guidance Clinic Treatment Program" was held at the American Orthopsychiatric Association meeting in Chicago on February 25, 1960. George Lytton, of Kansas City, Missouri, presided. Participants included Paul Benton, Tulsa, Oklahoma; Irwin Kraft, Houston, Texas; Hunter Comly, Detroit, Michigan; Leon Oettinger, Pasadena, California; and Norman Tolo, St. Joseph, Missouri.

Oettinger opened the program with a discussion of medication as it applies to the control of behavior, with special reference to its use in minimal brain-damaged children. It was his feeling that children with minimal brain damage and behavior disorders responded quite well to the administration of "psychotonic" drugs. He emphasized, however, that the dosage of these medications should be carefully adjusted to each individual child, and pointed out that many double-blind studies do not follow this rule.

Benton spoke of his clinical experiences in drug administration for behavior control in a psychiatric outpatient clinic. He pointed out that his previous experiences had been in a hospital setting, and mentioned that the control of behavior by medication was so successful in this setting that he moved to consideration of drug therapy with outpatients. He discussed the newer drugs that are being used, citing dosages, time of administration, and indications for their use.

Kraft spoke about research in psychopharmacology. He raised a great many ethical and moral questions concerning the use of drugs in children, while at the same time emphasizing that in his own clinical setting drugs were widely used in the treatment of behavior disorders, and that he wholeheartedly endorsed this practice. He felt that the question of long-range effects of psychiatric drugs should be investigated very thoroughly, and mentioned further that the question of the interplay of hormonal effects and medication should be investigated more intensively than it is at present, and in a great many more clinical settings.

Comly spoke about the historical aspects of drug administration, pointing out that prior to 1938 control of behavior was attempted by using drugs in the anesthetic series. Beginning in 1938 with the use of amphetamine and in 1952 with the use of the tranquilizers, the clinician had a new instrument in his psychotherapeutic armamentarium, and for the first time was able to affect certain portions of the brain without producing a state of mild anesthesia or intoxication. He also emphasized the importance of complete diagnostic study, and emphasized further the necessity of involving the family in the treatment process.

Tolo discussed the effects of medication for behavior disorder upon the family. He pointed out that it is possible for mothers to sabotage drug treatment unless they are involved in the treatment process. He spoke of some of the factors in the family interaction process which may affect the child, such as children acting out their mother's unconscious wishes, or children taking the brunt of a serious disagreement between parents. It was his feeling that children should not be placed on medication until a complete study of the child and his family had been made, and he stressed the importance of parental cooperation in this matter.

Following the individual presentations, the audience participated in a rather lively discussion of the theoretical aspects of some of these medications, and some discussion of the developmental process as it affects the younger child.

American Psychosomatic Society

The American Psychosomatic Society meetings were held in Montreal in late March.

Charles Shagass and Marvin Schwartz of the University of Iowa (Iowa City, Iowa) presented a paper on "Evoked Cortical Potentials and Sensation in Man." Shagass described a

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*Prepared on request by George Lytton, The Greater Kansas City Mental Health Foundation, Kansas City, Missouri.

recently constructed electronic instrument, called a "cortical summator," which measures averaged cortical potentials from scalp electrodes. He has measured cortical activity of normal subjects and patients under various conditions, including visual stimuli, somatosensory stimuli, and drugs. Using this technique, he has found individual differences in cortical activity. Herbert H. Jasper's discussion of the paper emphasized the importance of quantifying the variables in brain physiology.

Samuel Bogoch (Massachusetts Mental Health Center, Boston, Massachusetts) reviewed results of his series of "Neurochemical Studies on Schizophrenic and Affective Psychoses." Among other findings, he reported that his research has shown that the absolute concentration of bound neuraminic acid in the cerebrospinal fluid is lower in schizophrenics than in nonschizophrenics. Some of the complexities of this kind of research were discussed by R. A. Cleghorn (Allan Memorial Institute of Psychiatry, Montreal, Canada).

David R. Hawkins and his co-workers at the University of North Carolina Medical School, Chapel Hill, North Carolina, reported on their "Multivariant Psychopharmacologic Study in Normals." They gave chlorpromazine, dextro-amphetamine, meprobamate, amobarbital, and a placebo to a group of ten medical students, and measured the effects of drugs on various psychological tests and rating scales. Chlorpromazine was the most active drug, causing drowsiness, dysphoria, and mental clouding. Meprobamate had little activity. Amobarbital and dextro-amphetamine produced variable results, though, in general, amobarbital had a sedating effect and dextro-amphetamine an alerting effect. These investigators also found that the social situation was an important factor in the drug response, and that there were individual variations in response to the drugs. Among other comments, the discussant of this paper, Sydney Malitz (New York State Psychiatric Institute, New York City), reemphasized the need for thorough knowledge of the background and integrative life functioning of volunteer subjects and observed that conclusions should not be based on the premise that volunteer subjects are necessarily "healthy."

FORTHCOMING INTERNATIONAL SYMPOSIUM ON THE EXTRAPYRAMIDAL SYSTEM AND NEUROLEPTICS

The Department of Psychiatry of the University of Montreal is organizing an international symposium on "The Extrapyramidal System and Neuroleptics" to be held at the University of Montreal on November 17, 18, and 19, 1960. This symposium will permit an exchange of ideas among researchers interested in this subject from the point of view of anatomy, physiology, neurosurgery, and psychiatry. Admission to the symposium will be unrestricted, but participation will be by invitation only. The ten Canadian provinces, the United States, and several European countries will be represented. English and French will be the official languages, with simultaneous translation.

The papers and discussions are being organized around five major areas: anatomy and physiopathology, pharmacology, Parkinson's disease, extrapyramidal syndromes and clinical psychiatry, and psychodynamic aspects of neuroleptics. For further information write to Dr. Jean-Marc Bordeleau, Department of Psychiatry, University of Montreal, Montreal, Canada.

A NOTE ON THE OCCURRENCE OF "FALSE POSITIVES" IN RAPID URINE COLOR TESTS FOR PHENOTHIAZINE DRUGS*

The following note is an "addendum" to work which has been published by Drs. Irene S. and Fred M. Forrest. In order to reach interested researchers as quickly as possible, the note is printed here even though the findings are also being published.

During the past three years we have reported a number of rapid urine color tests for the various phenothiazine compounds. Further exploration of urine specimens obtained from different types of patients not usually seen in a Veterans Administration neuropsychiatric hospital has resulted in the finding of additional "false positives" which, varying with the type of patients, may occur more frequently than we originally indicated (although our original data on the absence of "false negatives" remain unchanged). Excluding all cases of weakly to frankly positive tests obtained with the more sensitive color tests 2, 3, and 4, after discontinuation of a phenothiazine drug for many weeks, and in some instances up to six months after drug discontinuation, the following false positives were encountered with the tests below:

1. Rapid urine color test for chlorpromazine, promazine, and mepazine (1, 2).
2. Rapid urine color test for triflupromazine (3).
3. Rapid urine color test for piperazine-linked phenothiazine drugs (4).
4. Rapid urine color test for the detection of small amounts of phenothiazine compounds (FPN [ferric chloride, perchloric acid, nitric acid], general test [5].)
5. Rapid urine color test for thioridazine (6).

Additional false positives which have been observed pertain mainly to tests 2 and 3, which are extremely sensitive and are suitable for the demonstration of traces (fractions of a gamma) of phenothiazine compound per ml. of urine. The high degree of sensitivity is obtained at the expense of a higher rate of false positives, some of which have been identified as follows:

A. Urine samples from patients on daily medication of 6 gm. or more of para-aminosalicylic acid showed false positives ranging from the trace to ++ levels in tests 1, 4, and 5, and from the + to +++ levels in tests 2 and 3. (See also references 4 and 6.)

B. Urine samples obtained from phenylketonuric patients showed false positives with tests 2 to 5, ranging from the trace to ++++ levels, the latter having been obtained with test 3 in a urine showing 80 to 100 mg. of phenylpyruvic acid according to the phenistix test. (See also reference 6.)

C. Urine samples from persons with impaired liver function—acute or chronic—may show false positives of trace to + intensity with tests 2, 3, and 4. (See also references 3, 4, 5, 6.)

D. Urine samples of patients on therapy with high doses of natural conjugated or synthetic estrogens have shown occasional false positives, of trace to + levels, with tests 2, 3, and 4.

E. Some infrequent false positives not attributable to any factor under A to D were found in control urine specimens of persons without any medication. In the absence of exact knowledge, it is assumed that biochemical agents so far unidentified (possibly steroids, ketones, phenolic, indolic, or hydroxylated pyridine derivatives) may account for these unex-

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*By Irene S. and Fred M. Forrest, Veterans Administration Hospital, Brockton, Massachusetts.

plained false positives. This hypothesis is advanced on the basis of color reactions obtained in vitro with relatively high concentrations of these compounds.

While the total incidence of false positives seen in our laboratories remained well below 10 per cent, other investigators have observed higher rates of false positives. Herbert S. Posner (St. Elizabeths Hospital, Washington, D. C.) has reported this in a personal communication. A paper by Jack Heyman (Central Islip State Hospital, Central Islip, New York) on a modification of test 3 appeared in the *American Journal of Psychiatry*, 1960, 116, 1108.

In spite of the occurrence of false positives, the tests constitute valuable diagnostic tools, if properly evaluated and interpreted in the light of these findings, especially since we have not seen false negative tests in any of the five different procedures mentioned above. In this connection it should be kept in mind that extreme urine dilutions after excessive fluid intake may give rise to very inadequate color reactions.

In all cases of apparent false negatives the tests should be repeated on another urine specimen, to be obtained 1 to 3 hours after carefully supervised administration of drugs, preferably in the form of liquid concentrates.

References

1. Forrest, Fred M., and Forrest, Irene S. A simple test for the detection of chlorpromazine in urine. *American Journal of Psychiatry*, 1957, 113, 931-932.
2. Forrest, Fred M., Forrest, Irene S., and Mason, Aaron S. A rapid urinary test for chlorpromazine, promazine and Pacatal: a supplementary report. *American Journal of Psychiatry*, 1958, 114, 931-932.
3. Forrest, Fred M., Forrest, Irene S., and Mason, Aaron S. A rapid urine color test for triflupromazine (Vesprin). *American Journal of Psychiatry*, 1959, 115, 1114-1115.
4. Forrest, Fred M., Forrest, Irene S., and Mason, Aaron S. A rapid semi-quantitative urine color test for piperazine-linked phenothiazine drugs (Compazine, Trilafon and analogous compounds). *American Journal of Psychiatry*, 1959, 116, 549-551.
5. Forrest, Irene S., and Forrest, Fred M. Urine color test for the detection of phenothiazine compounds. *Clinical Chemistry*, 1960, 6, 11-15.
6. Forrest, Irene S., Forrest Fred M., and Mason, Aaron S. A rapid urine color test for thioridazine (Mellaril, TP 21, Sandoz). *American Journal of Psychiatry*, 1960, 116, 928-929.

RESEARCH IN PSYCHOPHARMACOLOGY AT THE INSTITUTE OF PHARMACOLOGY IN MILAN, ITALY

A number of research projects relevant to psychopharmacology are being conducted at the Istituto di Farmacologia, Universita degli Studi di Milano, in Milan, Italy. From time to time, the Institute's chemotherapy staff publishes a newsletter on research in progress there, including the field of brain chemistry and the mode of action of centrally acting drugs as a main area of interest. Some of the projects currently under way at the Institute are briefly described in the following paragraphs:

Reserpine analogues. The effect of different drugs on brain serotonin, measured with a spectrofluorimetric method, is under investigation. Two analogues of reserpine—methyl-18-0-(3-NN-dimethylaminobenzoyl) reserpate or SU 5171 and carbethoxysyringoyl methylreserpate or SU 3118 (syrosingopine)—show selective pharmacological activity. SU 3118 is hypotensive, nonsedative, and inactive in releasing brain serotonin, while SU 5171 is sedative, releases serotonin, and does not have a hypotensive effect. Hypothermia and increase of

pentobarbital sleeping time parallel the changes in brain serotonin. Experiments are now planned to investigate effects of reserpine analogues on brain noradrenalin and dopamine.

Brain serotonin. In other experiments it has been shown that electroshock increases brain serotonin, particularly in the mesencephalic area. Imipramine can under certain conditions counteract the depletion of brain serotonin induced in rats by reserpine treatment. This effect is common also to chlorpromazine. The possibility that imipramine or chlorpromazine can interfere with the method of measuring serotonin is also considered. New potential inhibitors of monoamine oxidase are under evaluation using the following tests in rats: reserpine antagonism, tryptamine convulsions, serotonin hypothermia, and brain serotonin content.

Oxygen tension in brain. Oxygen tension in brain and other tissues is measured by means of the Cater and Silver apparatus. A decrease of oxygen tension with serotonin and reserpine and an increase with noradrenalin and phenylcyclopropylamine (SKF trans 385) have been observed by the use of electrodes implanted in the brain (hypothalamus).

Serotonin and absorption of Ca^{45}. Serotonin is active in increasing the absorption of $Ca^{45}Cl_2$ at the level of rat small intestine in vitro (using the everted intestinal sac technique). Serotonin, when added at the concentration of 20 μg./ml. to the perfusing solution, significantly increases the penetration of trace amounts of labeled calcium chloride after a 15-minute and 90-minute incubation time. Experiments in vivo are now planned to determine quantitatively whether this effect of serotonin may be observed at physiological concentrations. Radio-chemical and autoradiographic measurements have established that large doses of serotonin increase in vivo content of $Ca^{45}Cl_2$ in small intestine, blood, and brain. Absorption and distribution of $Ca^{45}Cl_2$ will also be studied in reserpine- and iproniazid-treated rats in order to determine the possible effect of largely modified tissue serotonin levels on calcium penetration.

Effect of serotonin in adrenalectomized rats. The increased toxicity of serotonin (more than 20 times) in adrenalectomized rats is due to hypothermia, hypotension, and fall of blood sugar. The administration of cortisone and DOCA produces a partial protection. Noradrenalin and adrenalin are not able to inhibit the increased toxicity of serotonin but temporarily reduce hypotension and to a lesser degree hypothermia. It was found that increasing room temperature up to 30°C did not inhibit the toxic effect of serotonin, even when hypothermia was reduced. Adrenalectomized mice show an even greater increase of toxicity to serotonin than adrenalectomized rats.

Hormones and brain serotonin. The correlation between hormonal treatments and brain serotonin is under investigation. Thyroxine and cortisone increase brain serotonin. Sex and age are also factors influencing brain serotonin.

Barbiturate effect. In other experiments, pretreatment with DOPA decreased sleeping time of pentobarbital whereas serotonin, under the same conditions, had a potentiating effect. Chlorpromazine also decreased sleeping time of pentobarbital if injected 48 hours before pentobarbital. It is possible that these effects could reflect the activity of microsome enzymes capable of oxidizing barbiturates.

Amino acids in brain. An analysis of brain amino acids after electroshock or Metrazol convulsions (rats) is in progress in connection with previous findings showing that electroshock increases brain NH_3. Amino acids are quantitatively determined according to the Stein and Moore technique. Particular attention will be paid to changes of glutamine acid, α, β, or γ amino N or iso-butyric acid.

This research represents a joint effort of the chemotherapy staff: S. Garattini, who is Chief of the Chemotherapy Staff and Deputy Chief of the Institute, A. Giachetti, R. Kato, A. Leonardi, B. Murelli, E. Mussini, V. Palma, P. Paoletti, R. Paoletti, and L. Valzelli.

RECENT NIMH GRANTS FOR PSYCHOPHARMACOLOGICAL RESEARCH

Between January 15 and June 15, 1960, the National Institute of Mental Health awarded the following grants in support of psychopharmacological research. (The April PSC Bulletin listed NIMH-supported projects in this area which were active as of January 15). Requests for detailed information about the research should be addressed to the principal investigator of the project.

Ego Impairment with LSD-25 and Schizophrenia (Grant MY-2251). William E. Mooney, University of Pittsburgh, Pittsburgh, Pennsylvania.

Metabolism of Biogenic Amines (Grant MY-3050). Robert A. Cleghorn and Theodore L. Sourkes, McGill University, Montreal, Canada.

Psychotropic Drugs and Autonomic Dysfunction (Grant MY-3561). Heinz O. Schild, Michael Shepherd, and Hannah Steinberg, University College London, London, England.

Performance as a Function of Drive Level and Range of Cues (Grant MY-3612). John N. Agnew, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

A Proposed Screening Test for Tranquilizing Compounds (Grant MY-3648). James Dinsmoor, Indiana University, Bloomington, Indiana.

Clinical Evaluation of New Chemotherapeutic Agents (Grant MY-3701). Ralph W. Buddington and Robert G. Heath, Tulane University, New Orleans, Louisiana.

Functional Cytology—Hypothalamus and Pituitary Gland (Grant MY-3744). Thaddeus Samarajski, Ohio State University, Columbus, Ohio.

Psychic and Motor Effects of Drugs Injected into Ventricles and Subarachnoid Space (Grant MY-3775). Harry H. Garner and Ulrico Sacchi, Chicago Medical School, Chicago, Illinois.

Social Behavior in Rats; Studies in Escape and Avoidance (Grant MY-3801A). Richard A. Littman, University of Oregon, Eugene, Oregon.

Profiles of Group Behavior—A Comparative Study of Tranquilizers (Grant MY-3826). Anton F. Heusler and George Ulett, St. Louis State Hospital, St. Louis, Missouri.

Five-Year Community Follow-Up of Discharged Patients (Grant MY-3868). Else B. Kris, New York State Department of Mental Hygiene, New York, New York.

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